Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 2. Derivatives of 7-(1*H*-Pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoic (-heptanoic) Acids

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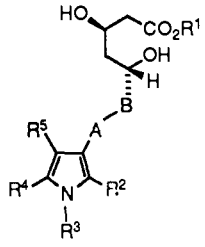
A series of 7-(1*H*-pyrrol-3-yl)-substituted-3,5-dihydroxyhept-6(*E*)-enoates (-heptanoates) **1** and **2** have been prepared and tested for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The most potent compounds exceeded mevinolin's activity in vitro and in vivo.

In continuation of our work on HMG-CoA reductase inhibitors with a central heterocyclic ring containing nitrogen atoms,[1] we report here on analogues **1** and **2** with a 1*H*-pyrrol-3-yl central moiety.



1 and **2**: $R^1 = CH_3$, H, Na;
A–B = (*E*)—CH=CH (**1**), CH_2CH_2 (**2**);
R^2–R^5 = see Table I

Chemistry

Compounds **1** cannot be obtained in reasonable yield by utilizing the glucose-derived "compactin aldehyde" **3**. This difference in behavior compared with pyridine and pyrimidine analogues[1] stems from the instability of pyrroles against acid-catalyzed hydrolysis. Instead, compounds **1** and **2**, respectively, were prepared from the appropriate aldehydes **4** (Scheme I). Compounds **4** were converted with >95% *E* selectivity to the corresponding α,β-unsaturated aldehydes **6**, by utilizing *cis*-(2-ethoxyvinyl)lithium according to Wollenberg.[2] Alternatively, some aldehydes **4** were converted by Emmons–Horner coupling with diisopropyl (cyanomethyl)phosphonate to the α,β-unsaturated nitriles **5**. Compounds **5** were reduced and then hydrolyzed to aldehydes **6**. Addition of the dianion of methyl acetoacetate gave the racemic β-keto-δ-hydroxy esters **7**. Highly stereoselective reduction of the keto group[3,4] was conducted with triethylborane and sodium borohydride to give methyl β,δ-dihydroxy carboxylates **1**, $R^1 = CH_3$.

Catalytic hydrogenation of **1** led to **2**. Saponification of the methyl esters **1** and **2** gave the corresponding sodium salts **1** and **2** (R^1 = Na), respectively.

Selected examples of these racemic sodium salts **2** were also synthesized in optically active form **13**, having the biologically active configuration 3*R*,5*R* (Scheme II). It should be emphasized that **2** and **13** are structurally identical, except for the ratio of the two enantiomers. They have been assigned different numbers for the sake of unambiguous differentiation in tables with biological results.

Aldehydes **6** were subjected to a highly stereoselective aldol reaction,[5,6] using the dianion **8** (generated from (*S*)-(−)-phenyl 2-hydroxy-2,2-diphenylacetate[7] and 2 equiv of LDA) to give **9**. In all cases, the indicated 3(*S*)-hydroxy isomer **9** exceeded its undesired 3*R* diastereomer by more than 96:4 (HPLC). Compound **9** was transformed into the corresponding methyl ester **10** with sodium in methanol. Reaction of **10** with 4 equiv of the enolate of *tert*-butyl acetate yielded the *tert*-butyl β-keto-δ-(*S*)-hydroxy carboxylate **11**, which was transformed to 3(*R*),5(*R*)-dihydroxyheptanoate **13** (R^1 = *t*-Bu) in analogy to the racemic ester **7** described above.

As shown by the HPLC analysis, **13** exceeded its undesired 3*S*,5*R* diastereomer by more than 96:4. Additionally according to ^{1}H NMR (Eu(hfc)$_3$) analyses, **13** had an optical purity of more than 92% ee. Saponification of the *tert*-butyl ester **13** gave the corresponding sodium salt (**13**, R^1 = Na).

The sodium salts of the olefins **1** (A–B = (*E*)-HC=CH) are acid sensitive while the hydrogenated analogues **2** (A–B = CH_2CH_2) are perfectly stable. When the olefinic methyl esters **1** ($R^1 = CH_3$) or their precursors **7** were dissolved in $CDCl_3$ that had not been filtered through basic alumina immediately before use, they decomposed very quickly, while **2** was stable. Likewise, the olefinic compounds **1** and **7** decomposed when chromatographed through silica gel in the absence of triethylamine, while the saturated analogue **2** was stable. Protolytic removal of the 5-hydroxy group of **1** leads to a cation that has a highly stabilizing resonance structure with a positively charged tetravalent nitrogen when A–B = HC=CH, but not when A–B = CH_2CH_2.

Aldehydes **4** were prepared following several synthetic routes as outlined in Schemes III–VI.

On the basis of the work of Gómez-Sanchez et al.,[8] substituted nitroethenes **15** were reacted with 2 equiv of β-keto esters **16**[9] to give the hydroxylamines **17**. Upon heating **17** with primary amines, especially anilines, the pyrrolecarboxylic acid esters **18** were obtained; they gave aldehydes **4** after reduction/oxidation (Scheme III).

According to H. Meyer[10] pyrrole esters **18** or **21** could also be prepared by cyclocondensation of nitroethenes **15**

(1) Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* Preceding paper in this issue.
(2) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365.
(3) Kathawala, F. G.; Prager, B.; Prasad, K.; Repič, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.
(4) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.
(5) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.
(6) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397.
(7) Commercially available as (*S*)-(−)-HYTRA from Merck-Schuchhardt, West-Germany.
(8) Gómez-Sanchez, A.; Stiefel, B. M.; Fernández, R.; Pascual, C.; Bellanato, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 441.
(9) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* **1948**, *70*, 2884.
(10) Meyer, H. *Liebigs Ann. Chem.* **1981**, 1534.

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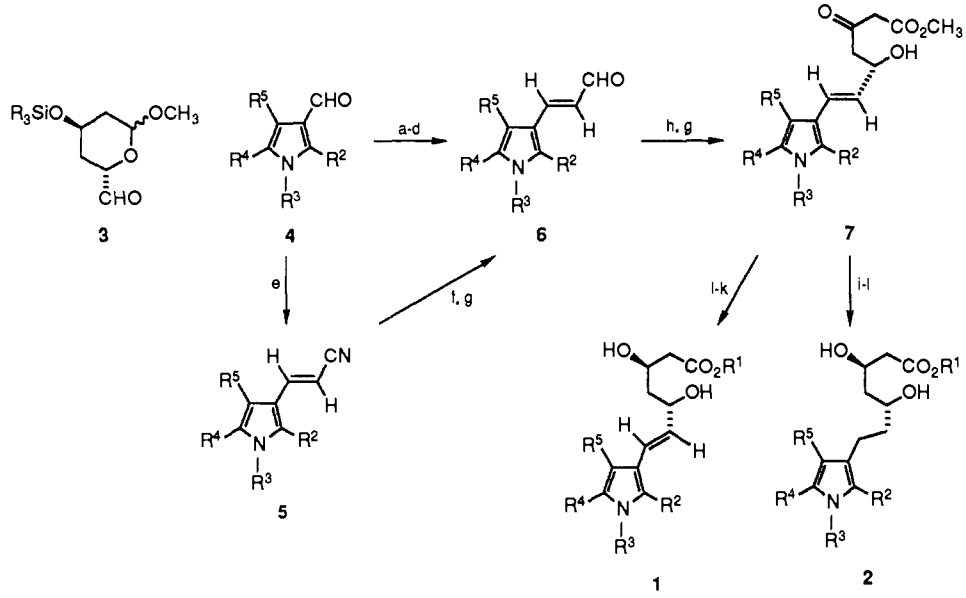
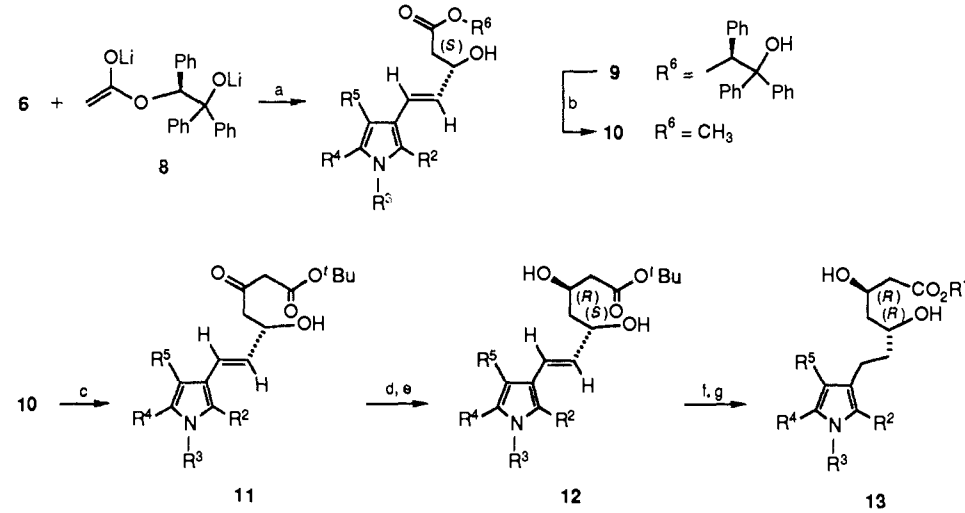
Scheme I[a]



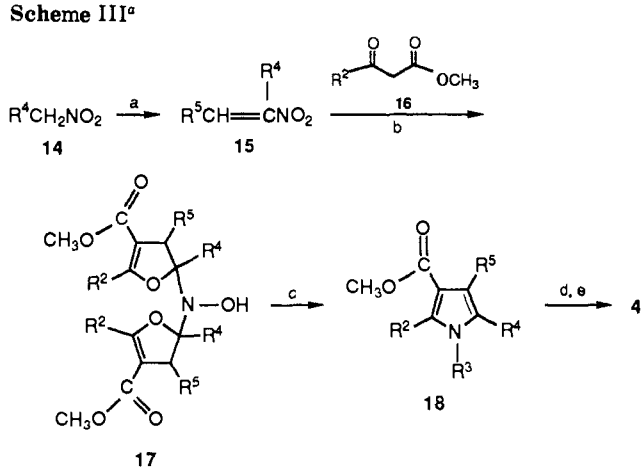
[a] (a) EtOCH=CHSn(*n*-Bu)$_3$;[2] (b) *n*-BuLi/−70 °C; (c) NH_4Cl/H_2O; (d) $TsOH/H_2O$; (e) $NCCH_2PO(O\text{-}i\text{-}Pr)_2/NaH$/0 °C; (f) $(i\text{-}Bu)_2AlH$; (g) NaH_2PO_4/H_2O; (h) $CH_3COCH_2CO_2CH_3/NaH/n\text{-}BuLi$/−15 °C; (i) Et_3B; (j) $NaBH_4$/−75 °C; (k) $NaOH/H_2O/CH_3OH$; (l) $Pd/C/H_2$.

Scheme II[a]



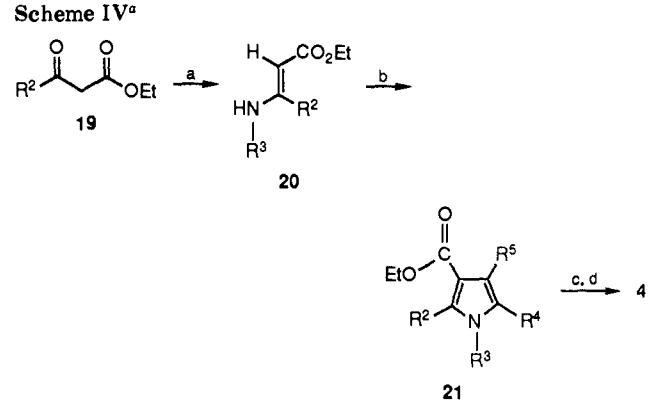
[a] (a) THF/−80 to −90 °C, 2 h; (b) 0.5 equiv of $NaOCH_3/CH_3OH$/23 °C; (c) 4 equiv of $CH_3CO_2{}^tBu$/4 equiv of LDA, −30 °C; (d) 1.05 equiv of Et_3B/24 equiv of CH_3OH in THF/−70 °C; (e) (1) 1.3 equiv of $NaBH_4$/−70 °C, (2) CH_3OH/25 °C; (f) $Pd/C/H_2$; (g) $NaOH/H_2O/CH_3OH$/12 h.

Scheme III[a]



[a] (a) R^5CHO; (b) $NaOCH_3$; (c) R^3NH_2/Δ; (d) $LiAlH_4$; (e) MnO_2.

Scheme IV[a]

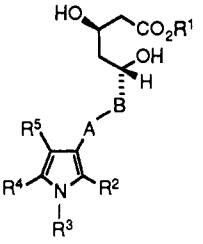


[a] (a) $R^3NH_2/AcOH/-H_2O$; (b) **15**/Δ; (c) $LiAlH_4$; (d) MnO_2.

with enamino esters **20** (Scheme IV). When substituent R^2 was not sterically demanding (e.g. $R^2 = CH_3$), **20** were easily obtained by addition of 1 equiv of amine to the β-keto ester **19** under acid catalysis.

However, when R^2 was bulky (e.g. R^2 = isopropyl), amines R^3NH_2 (especially anilines) attacked the ester

Table I. Inhibition of Solubilized Rat Liver HMG-CoA Reductase in Vitro[a] for Compounds of the General Structure 1,[c] 2,[c] and 13[d]

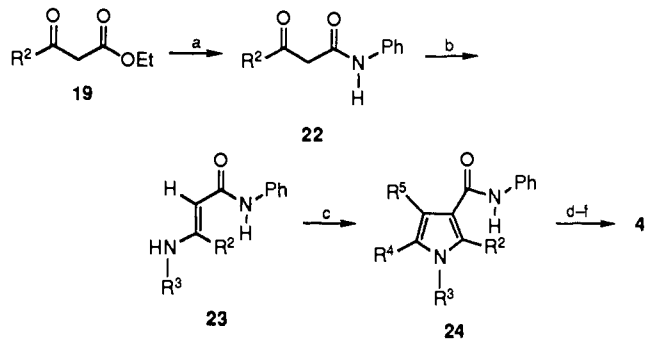


1[c], 2[c], and 13[d]

no.	R^1	R^2	R^3	R^4	R^5	A–B	formula	anal.[e]	IC_{50},[f] nM	rel[g] pot.
1a	Na	CH_3	Ph	H	*p*-C_6H_4F	CH=CH	$C_{24}H_{23}FNO_4Na$	C, H, N	65	12
1b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH=CH	$C_{26}H_{27}FNO_4Na$	C, H, N	7	110
2b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH_2CH_2	$C_{26}H_{29}FNO_4Na$	C, H, N	6	128
13b	Na	*i*-Pr	Ph	H	*p*-C_6H_4F	CH_2CH_2	$C_{26}H_{29}FNO_4Na$	C, H, N	3	257
1c	Na	CH_3	Ph	CH_3	*p*-C_6H_4F	CH=CH	$C_{25}H_{25}FNO_4Na$	C, H, N	250	3
2c	Na	CH_3	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{25}H_{27}FNO_4Na$	C, H, N	70	11
1d	Na	CH_3	*i*-Pr	H	*p*-C_6H_4F	CH=CH	$C_{21}H_{25}FNO_4Na$	C, H, N	330	2
2d	Na	CH_3	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{21}H_{27}FNO_4Na$	C, H, N	100	9
1e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH=CH	$C_{23}H_{29}FNO_4Na$	C, H, N	117	6
2e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{23}H_{31}FNO_4Na$	C, H, N	18	42
13e	Na	*i*-Pr	*i*-Pr	H	*p*-C_6H_4F	CH_2CH_2	$C_{23}H_{31}FNO_4Na$	C, H, N	9	85
1f	Na	*i*-Pr		H	*p*-C_6H_4F	CH=CH	$C_{26}H_{33}FNO_4Na$	C, H, N	69	12
2f	Na	*i*-Pr		H	*p*-C_6H_4F	CH_2CH_2	$C_{26}H_{35}FNO_4Na$	C, H, N	9	92
1g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH=CH	$C_{27}H_{29}FNO_4Na$	C, H, N	6	125
2g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{27}H_{31}FNO_4Na$	C, H, N	5	149
13g	Na	*i*-Pr	Ph	CH_3	*p*-C_6H_4F	CH_2CH_2	$C_{27}H_{31}FNO_4Na$	C, H, N	2.5	300
mevinolin							$C_{24}H_{37}O_6Na$		8	100

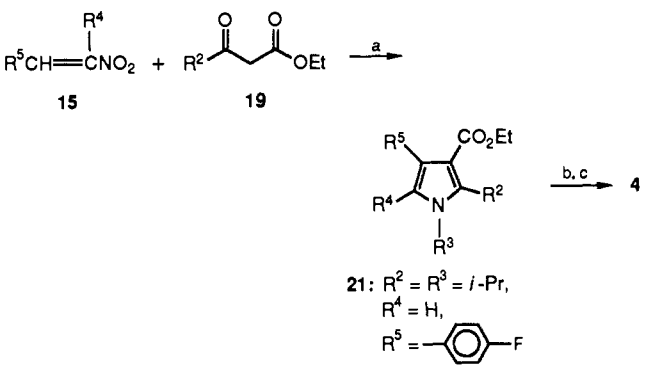
[a] The assay system described in ref 1 was used. [b] Ring-opened sodium dihydroxy carboxylate form, optically pure. [c] Racemic. [d] Optically active 3*R*,5*R* configuration. [e] Analytical results were within ±0.4% of the theoretical value. [f] IC_{50} values were determined by using four or five concentrations of each inhibitor. [g] For estimation of relative inhibitory potencies, mevinolin was assigned a value of 100. The IC_{50} value of test compound was compared with that of mevinolin, corrected for the somewhat different molecular weight.

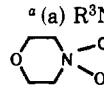
Scheme V[a]



[a] (a) $PhNH_2$/AcOH; (b) R^3NH_2/AcOH/$-H_2O$; (c) 15/Δ; (d) NaH/CH_3I/toluene/Δ; (e) $LiAlH_4$/Δ; (f) CrO_3/pyridine.

Scheme VI[a]



[a] (a) R^3NH_2/CH_3OH/25 °C/1 day; (b) $LiAlH_4$; (c) 4 equiv of  /0.02 equiv of $(Ph_3P)_3RuCl_2$.

functionality much faster than the keto group of **19**. In this case, it was necessary to preform the anilides **22** (Scheme V). Addition of aliphatic or aromatic primary amines R^3NH_2 to **22** under acid catalysis gave **23**, which were cyclocondensed with nitroethenes **15** to give 3-pyrrolecarbanilides **24**. While amides on LAH reduction usually lead to the corresponding amines, carbanilides **24** could be reduced to the corresponding aldehydes **4** via N-methylation, LAH treatment, and subsequent oxidation.

A new three-component coupling reaction allowed a one-pot synthesis of ethyl 1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (**21**, Scheme VI).

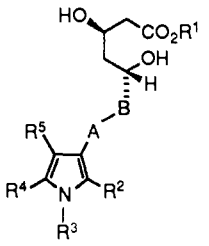
When a methanolic solution of β-nitro-*p*-fluorostyrene (**15**: R^4 = H, R^5 = *p*-C_6H_4F), β-keto ester **19** (R^2 = *i*-Pr), and isopropylamine was stirred at ambient temperature, the pyrrole ester **21** was obtained in 50% yield. LAH reduction followed by ruthenium(II)-catalyzed oxidation of the alcohol with *N*-methylmorpholine-*N*-oxide[11] gave the corresponding aldehyde **4**. This convenient three-component coupling may also be applicable for the syntheses of pyrrole esters **21** with other substitution patterns for R^2–R^5.

Biological Results and Discussion

The racemic sodium salts (**1** and **2**, R^1 = Na) as well as the optically active sodium salts **13** (R^1 = Na) were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase in vitro (Table I) and

(11) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *29*, 2503.

Table II. Inhibition of Cellular HMG-CoA Reductase in Cultures of HEP G2 Cells[a] for Sodium Salts of the General Formula 1[c] and 2[c]



1[c] and 2[c]

	IC_{50},[d] μM	relative[e] potency
mevinolin[b]	0.05	100
1a	0.83	6
1b	0.014	350
2b	<0.01	>500
1c	5.0	1
2c	0.57	9
1d	6.0	1
2d	0.27	19
1e	0.05	100
2e	0.002	2500
1f	0.106	47
2f	0.018	275

[a] Assay described in the preceding paper.[1] [b] Ring-opened sodium dihydroxy carboxylate form, optically pure. [c] Racemic. For definition of R^1–R^5 and A–B see Table I. [d] IC_{50} values varied somewhat for different batches of cells. Mevinolin sodium salt averaged $IC_{50} = 5 \times 10^{-8}$ M and was used in every run as an internal standard. The measured IC's for test compounds 1 and 2 were corrected for deviations of mevinolin's IC from its average value. [e] Mevinolin was assigned a value of 100. Potencies were obtained by comparison of racemic test compounds 1 or 2 with the internal standard mevinolin.

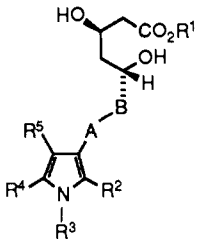
to inhibit *cellular* HMG-CoA reductase in cultures of hepatic cells (HEP G2, a human hepatoma cell line), as determined by the inhibition of the incorporation of sodium [^{14}C]acetate into cholesterol (Table II).

Selected compounds were evaluated for their ability to inhibit hepatic cholesterol "de novo" synthesis in male rats after po administration, as determined by the inhibition of the incorporation of sodium [^{14}C]octanoate[12] into hepatic cholesterol (Table III).

Selected compounds were further evaluated for their ability to decrease plasma cholesterol levels in normolipemic rabbits and dogs after po administration.

All tests were also conducted under the same experimental conditions with optically pure mevinolin. The respective results are included in Tables I–III. For substitution patterns "**b**", "**e**", and "**g**", we prepared and tested the racemic **2** as well as the optically active 3*R*, 5*R* sodium salt **13**. Optically active compounds **13** proved to have twice the potency in HMG-CoA reductase inhibition than the structurally identical but racemic **2** (Table I). This result was expected, since the antipode of the configuration drawn for **1**, **2**, and **13**, is biologically inactive.[13]

Table III. Inhibition of Hepatic Cholesterol "De Novo" Synthesis in Vivo (Rat, Orally)[a]



1 and 2

	% cholesterol "de novo" synthesis	relative potency
no drug	100	
mevinolin[b]	14	100
1b[c]	5.5	255
2b[c]	5.6	250
2e[c]	9	156
2f[c]	6.0	233

[a] Assay described in ref 16. [b] Lactone form, optically pure, 5 mg/kg bw. [c] Racemic sodium salts, 10 mg/kg bw. For definition of R^1–R^5 and A–B see Table I.

For better comparison of structure–activity relationships in **1** and **2** as well as with extensive work on analogues of the phenolic type (isocyclic central aromatic, A = oxygen, B = CH_2),[14,15] R^5 was kept constant as *p*-fluorophenyl.

The work on analogues of the phenolic type[14,15] has shown that alkyl substitution of the second ortho position is essential and leads to optimal biological activity for an isopropyl substituent.

We concentrated on R^2 = methyl or isopropyl, since ortho substituents smaller (methyl, ethyl, longer *n*-alkyl) or larger (cyclopentyl, *tert*-butyl) than the isopropyl group decreased activity in analogues of the phenolic type[14,15] and since halogen substituents (Cl, Br) led to good activity but increased toxicity.

Table I shows that the isopropyl derivatives were more potent than the methyl derivatives by a factor of 10–40 (e.g. **1b** vs **1a**, **1g** vs **1c**, **2g** vs **2c**).

There is much tolerance concerning R^3. Variation of R^3 (Ph, *i*-Pr, cyclohexyl) led to only small activity changes (e.g. **2b** vs **2e** vs **2f**, **1b** vs **1e** vs **1f**, **1a** vs **1d**).

Substitution of R^4 = hydrogen for a methyl group either slightly decreased (e.g. **1a** vs **1c**) or slightly increased (**2b** vs **2g** and **1b** vs **1g**) activity, depending on the nature of the other substituents. Hydrogenation of the trans olefinic bridge (A–B = (*E*)-HC=CH) had little influence on the biological activity of **1** in vitro (e.g. **1b** vs **2b**, **1c** vs **2c**, **1d** vs **2d**, **1e** vs **2e**, **1f** vs **2f**, **1g** vs **2g**); however, the hydrogenated derivatives **2** were much less acid sensitive (vide supra) and much more active in vivo.

In the HEP G2 cell-test (Table II) the racemic compounds **1b**, **2b**, and **2e** are 3.5, 5.0, and 25 times, respectively, more active than optically pure mevinolin sodium salt of the same concentration. General trends in Tables I and II are comparable. The superiority of **1b**, **2b**, and

(12) Dietschy, J. M.; McGarry, J. D. *J. Biol. Chem.* **1974**, *249*, 52. Andersen, J. M.; Dietschy, J. M. *J. Lipid Res.* **1979**, *20*, 740. Stange, E. F.; Dietschy, J. M. *J. Lipid Res.* **1983**, *24*, 72.

(13) 3-epi, 5-epi, and 3,5-bis epi isomers of compactin and mevinolin have been reported to be biologically inactive: Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858. Stokker, G. E.; Rooney, C. S.; Wiggins, J. M.; Hirshfield, J. J. *J. Org. Chem.* **1986**, *51*, 4931. The biological inactivity of synthetic compactin analogues with 3*S* configuration has also been reported: Lee, T.-J. *Trends Pharmacol. Sci.* **1987**, *8*, 442 and references cited therein.

(14) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Wess, G. International Symposium on Cholesterol Control And Cardiovascular Diseases: Prevention And Therapy, Milan (Italy) July 7–9, 1987; Abstract book page 133.

(15) European Application 0216 127, 1987.

(16) Dietschy, J. M.; Spady, D. K. *J. Lipid Res.* **1984**, *25*, 1469. Alfin-Slater, R. B.; Deuel, H. J., Jr.; Scholtz, M. C.; Shimoda, F. K. Group Report No. N3, 1950; University of Southern California, Consolidated Eng. Corp.

especially **2e** compared with mevinolin is more pronounced in the cell test. Inhibition of hepatic cholesterol "de novo" synthesis in vivo by oral **1b** or **2b** is about 2.5 times stronger than that for mevinolin (Table III). In normally fed rabbits (n = 6), 20 mg/kg racemic **2b** decreased total plasma cholesterol levels by 34% after oral administration for 10 days (optically pure mevinolin at 10 mg/kg for 10 days, 25%), while **1b** was totally inactive under the same conditions. The reason for the lack of activity of **1b** in the rabbit experiment is currently not known.[22] The chemically demonstrated acid sensitivity of **1b** (vide supra) would suggest that, contrary to **2b**, **1b** may not survive the stomach passage. However this view is not consistent with the comparable activity of **1b** and **2b** to inhibit hepatic cholesterol "de novo" synthesis in rats after po administration (Table III). In normally fed rabbits (n = 4), 10 mg/kg racemic **2e** decreased total plasma cholesterol levels by 42% after oral administration for 6 days (optically pure mevinolin at 10 mg/kg for 6 days, 25%).[17,18]

In normally fed male beagle dogs (n = 4), 20 mg/kg racemic **2b** decreased LDL-cholesterol levels by 48% and increased HDL-cholesterol levels by 14% after oral administration for 14 days (optically pure mevinolin at 10 mg/kg for 19 days: LDL-cholesterol −18%, HDL-cholesterol +2%).[18]

In conclusion, some compounds of general formula **2** exceeded mevinolin in their ability to inhibit HMG-CoA reductase in vitro and to inhibit cholesterol biosynthesis in vivo. They are promising candidates for development as antiarterosclerotic agents.

Experimental Section

For general remarks see the preceding paper in this issue.[1] ^{1}H NMR spectra were recorded in $CDCl_3$, unless noted otherwise. All starting materials were commercially available unless indicated otherwise.

1-(*p*-Fluorophenyl)-2-nitropropene (15). A solution of *p*-fluorobenzaldehyde (84 g), nitroethene (69.4 g), and *n*-butylamine (4 mL) in xylol (110 mL) was refluxed for 20 h under a Dean–Stark trap. On cooling to 0 °C, 21.7 g of the product crystallized (mp 64–65 °C). To the filtrate were added nitroethene (41.4 g) and *n*-butylamine (3 mL), and the solution was refluxed for 14 h under a Dean–Stark trap. The solution was evaporated in vacuo and the residue was digerated with methanol at 0 °C, until crystallization occurred. The crystals were collected and washed with cold methanol (53.8 g, mp 65–66 °C). Anal. ($C_9H_8FNO_2$) C, H, F, N.

Ethyl 3-(Phenylamino)-but-2(*E*)-enoate (20). A solution of aniline (45.5 mL, 0.5 mol), ethyl acetoacetate (63.5 mL, 0.5 mol), and glacial acetic acid (1 mL) in toluene (100 mL) was refluxed for 4 h under a Dean–Stark trap. The solvent was evaporated and the residue was distilled to give 57.9 g of colorless oil: bp 118–120 °C (1.5 mm); MS $C_{12}H_{15}NO_2$ m/e = 205 (M^+). Anal. ($C_{12}H_{15}NO_2$) C, H, N.

***N*,*N*-Bis[3-(4-fluorophenyl)-4-(methoxycarbonyl)-5-methyl-2,3-dihydrofuran-2-yl]hydroxylamine (17).** To a stirred solution of sodium methanolate (2.92 g, 54 mmol) in methanol (54 ml) was added methyl acetoacetate (20.9 g, 180 mmol) dropwise at 0 °C followed by 4-fluoro-β-nitrostyrene[19] (30.1 g, 180 mmol). After 15 min, a thick mash formed that was allowed to stand for 2 h at 0 °C. The solid was collected by suction, washed with ice-cold methanol, and dried over P_4O_{10} in vacuo to give 22.0 g of colorless solid: mp 139–141 °C; 7.0 g of product were obtained from the mother liquor; NMR δ 2.25 (6 H, s), 3.32 (3 H, s), 3.50 (3 H, s), 4.30 (2 H, dd), 5.40 (2 H, d), 7.16 (8 H, d), 8.72 (1 H, s); MS $C_{26}H_{25}F_2NO_7$ FAB m/e = 502 ($M + H^+$), 458, 235. Anal. ($C_{26}H_{25}F_2NO_7$) C, H, F, N.

1-Phenyl-2-methyl-3-(methoxycarbonyl)-4-(4-fluorophenyl)-1*H*-pyrrole (18a). Aniline (5.59 g, 60 mmol) was added to a solution of hydroxylamino compound **17** (15 g, 30 mmol) in ethanol (600 mL). The mixture was refluxed for 24 h. Aniline (1.1 g) was added and the mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was distributed between dichloromethane and 1 N hydrochloric acid. The organic layer was washed with saturated sodium bicarbonate solution and then with brine, dried, and concentrated. The residue was chromatographed with *n*-hexane/ether/dichloromethane (16:3.5:0.5) over silica, giving 4.0 g of reddish, thick oil: NMR δ 2.43 (3 H, s), 3.70 (3 H, s), 6.70 (1 H, s), 6.87–7.66 (9 H, m); MS $C_{19}H_{16}FNO_2$ m/e = 309 (M^+), 278, 248. Anal. ($C_{19}H_{16}FNO_2$) C, H, F, N.

1-Isopropyl-2-methyl-3-(methoxycarbonyl)-4-(4-fluorophenyl)-1*H*-pyrrole (18d). Isopropylamine (3.6 g, 60 mmol) was added to a suspension of hydroxylamino compound **17** (15 g, 30 mmol) in methanol (500 mL). The suspension was heated for 2 h at 40 °C and for 5 h at 50 °C, changing to a clear solution. The solvent was removed in vacuo and the residue was chromatographed with *n*-hexane/ether (4:1) over silica to yield 7.3 g of pale reddish crystals: mp 97–99 °C; NMR δ 1.42 (6 H, d), 2.53 (3 H, s), 3.65 (3 H, s), 4.37 (1 H, sept.), 6.60 (1 H, s), 6.80–7.46 (4 H, m); MS $C_{16}H_{18}FNO_2$ m/e = 275 (M^+), 244, 202, 201. Anal. ($C_{16}H_{18}FNO_2$) C, H, F, N.

Ethyl 1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (21c). A solution of **20** (23.1 g, 113 mmol) and **15** (20.5 g, 113 mmol) in ethanol (250 mL) was refluxed for 30 h. The solvent was evaporated in vacuo and the residue was chromatographed over silica (1 kg) with cyclohexane/ethyl acetate (95:5) to give 26.0 of a colorless oil: NMR δ 1.05 (3 H, t), 1.85 (3 H, s), 2.3 (3 H, s), 4.1 (2 H, q), 6.9–7.6 (9 H, m); MS $C_{21}H_{20}FNO_2$ m/e = 337 (M^+), 308, 292. Anal. ($C_{21}H_{20}FNO_2$) C, H, F, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxaldehydes 4 from Substituted 3-(Alkoxycarbonyl)-1*H*-pyrroles 18 or 21. General Procedure. A solution of ester **18** or **21** (82 mmol) in ether (150 mL) was added dropwise at 0–5 °C to the stirred suspension of lithium aluminum hydride (7.8 g, 200 mmol) in ether (300 mL). The suspension was stirred for 1 h at 0 °C and then for 2 h at room temperature. At 0 °C, 35 mL of ethyl acetate and then 16 mL of water followed by 24 mL of 2 N aqueous sodium hydroxide were added dropwise. The suspension was stirred for 30 min at room temperature and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over 1 kg of silica with cyclohexane/ethyl acetate (2:1) containing 0.2% triethylamine (yield 85–95%).

To a solution of the substituted 3-(hydroxymethyl)pyrrole (70 mmol) in ether (1.2 L) and triethylamine (12 mL) was added activated manganese dioxide (182.5 g). The suspension was stirred at room temperature under nitrogen. After 24 h, the same amount of manganese dioxide was added. After 24 h the solid was removed and washed with ether. The filtrates were concentrated in vacuo; the residue was chromatographed over silica with cyclohexane/ethyl acetate (6:1) containing 0.1% triethylamine (yield 65–85%).

1-Phenyl-2,5-dimethyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: colorless oil, crystallizing on standing; NMR δ 1.3 (1 H, br s), 2.0 (3 H, s), 2.1 (3 H, s), 4.55 (2 H, s), 6.9–7.65 (9 H, m); MS $C_{19}H_{18}FNO$ m/e = 295 (M^+), 278 (M^+ − OH). Anal. ($C_{19}H_{18}FNO$) C, H, F, N.

1-Phenyl-2-methyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: pale yellow, resinous solid; NMR δ 1.5 (1 H, br s), 2.26 (3 H, s), 4.63 (2 H, s), 6.87 (1 H, s), 6.93–7.70 (9 H, m); MS $C_{18}H_{16}FNO$ m/e = 281 (M^+), 264 (M^+ − OH). Anal. ($C_{18}H_{16}FNO$) C, H, F, N.

1-Isopropyl-2-methyl-3-(hydroxymethyl)-4-(fluorophenyl)-1*H*-pyrrole: colorless oil; MS $C_{15}H_{18}FNO$ m/e = 247 (M^+ − OH), 188. Anal. ($C_{15}H_{18}FNO$) C, H, F, N.

1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4a): yellow, resinous solid; NMR δ 2.50 (3 H, s), 6.80 (1 H, s), 6.85–7.70 (9 H, m), 10.03 (1 H, s); MS $C_{18}H_{14}FNO$ m/e = 279 (M^+), 278 (M^+ − H). Anal. ($C_{18}H_{14}FNO$) C, H, F, N.

1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4c): yellow solid; NMR δ 1.94 (3 H, s), 2.35 (3 H, s), 6.95–7.7 (9 H, m), 9.85 (1 H, s); MS $C_{19}H_{16}FNO$ m/e =

(17) Hypocholesterolemic activity in rabbits was tested following the protocol described in ref 1.
(18) Hypocholesterolemic activity in animal studies will be described in detail in a future publication.
(19) Gattermann-Wieland *Die Praxis des Organischen Chemikers*, 43rd ed.; W. de Gruyter: Berlin, 1982; p 361.

293 (M^+). Anal. ($C_{19}H_{16}FNO$) C, H, F, N.

1-Isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4d): colorless oil; NMR δ 1.43 (6 H, d), 2.60 (3 H, s), 4.30 (1 H, sept), 6.68 (1 H, s), 6.9–7.56 (4 H, m), 9.92 (1 H, s); MS $C_{15}H_{16}FNO$ m/e = 245 (M^+), 202. Anal. ($C_{15}H_{16}FNO$) C, H, F, N.

3-Oxo-4-methylpentanoic Acid Anilide (22). A solution of ethyl 3-oxo-4-methylpentanoate[9] (47.4 g, 0.3 mol), aniline (27.93 g, 27.3 mL, 0.3 mol), and acetic acid (0.6 mL) in toluene (360 mL) was refluxed for 4 h with a Dean–Stark trap. The cold mixture was washed twice with 0.5 N hydrochloric acid, twice with saturated sodium bicarbonate solution, once with brine, dried, concentrated, and chromatographed with toluene/ethyl acetate (10:1) over 1 kg of silica, giving 40.5 g (66% yield) of a pale pink oil: NMR δ 1.2 (6 H, d), 2.8 (1 H, sept), 3.65 (2 H, s), 7.0–7.75 (5 H, m), 9.1–9.4 (1 H, br s); MS $C_{21}H_{15}NO_2$ m/e = 205 (M^+), 93. Anal. ($C_{21}H_{15}NO_2$) C, H, F, N.

3-(Phenylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23b). A solution of ethyl 3-oxo-4-methylpentanoate[9] (31 mL, 0.2 mol), aniline (37 mL, 0.41 mol), and acetic acid (1.0 mL) in toluene (50 mL) was refluxed for 6 h with a Dean–Stark trap. The solvent was removed in vacuo. On cooling the residue crystallized. It was recrystallized from toluene/petroleum ether (80–110 °C) (2:1) to yield 38.7 g of colorless solid: mp 147–148 °C; a second crop of crystals can be obtained from the mother liquor; NMR δ 1.1 (7 H, d + m), 2.9 (1 H, sept), 4.75 (1 H, s), 6.8–7.6 (10 H, m), 11.1 (1 H, br s). Anal. ($C_{18}H_{20}N_2O$) C, H, N.

3-(Isopropylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23e). To a solution of anilide **22** (35.7 g, 174 mmol) and acetic acid (0.6 mmol) in toluene (600 ml), refluxing under a Dean–Stark trap, was added isopropylamine (20.6 g, 348 mmol) dropwise over 3 h. The mixture was refluxed for 16 h, concentrated in vacuo, and cooled, leading to crystallization. The solid was digerated with diisopropyl ether/petroleum ether (1:1), collected with suction filtration, and washed with petroleum ether, giving 28.9 g of colorless solid: mp 152–153 °C; NMR δ 1.1 (6 H, d), 1.25 (6 H, d), 2.73 (1 H, sept), 3.8 (1 H, m), 4.43 (1 H, s), 6.7 (1 H, s), 6.9–7.6 (5 H, m), 9.1–9.6 (1 H, br s); MS $C_{15}H_{22}N_2O$ CI m/e = 247 (M + H^+), 154. Anal. ($C_{15}H_{22}N_2O$) C, H, N.

3-(Cyclohexylamino)-4-methylpent-2(*E*)-enoic Acid Anilide (23f). A solution of anilide **22** (31.6 g, 154 mmol), acetic acid (1.5 mL), and cyclohexylamine (30.55 g, 308 mmol) in toluene (750 mL) was refluxed for 20 h under a Dean–Stark trap. The solvent was removed in vacuo, the residue was swirled with 150 mL of diisopropyl ether, collected with suction filtration, and washed with petroleum ether to give 27.1 g of a colorless solid (an addition 8.9 g came from the mother liquor): yield 82%; mp 123–132 °C; NMR δ 1.15 (6 H, d), 1.0–2.1 (10 H, m), 2.7 (1 H, sept), 3.45 (1 H, m), 4.4 (1 H, s), 6.55 (1 H, m), 6.9–7.6 (5 H, m), 9.5 (1 H, br s) MS $C_{18}H_{26}N_2O$ m/e = 286 (M^+), 194, 93. Anal. ($C_{18}H_{26}N_2O$) C, H, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxanilides 24 from Enamino Anilides 23. General Procedure. A solution of the nitro olefin **15** (95 mmol) and enamino carboxanilide **23** (100 mmol) in ethanol (300 mL) was refluxed for 12 h under nitrogen. Most of the solvent was removed in vacuo. Cooling of the residue in an ice bath gave crystals that were swirled in cyclohexane/ethyl acetate (200 mL), collected, and recrystallized.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24b): yield 78%; mp 192–194 °C (from methanol); NMR δ 1.30 (6 H, d), 3.14 (1 H, sept), 6.73 (1 H, s), 7.00–7.70 (10 H, m). Anal. ($C_{26}H_{23}FN_2O$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24e): yield 50%; mp 131–133 °C (not recryst); NMR δ 1.45 (6 H, d), 1.55 (6 H, d), 3.75 (1 H, sept), 4.6 (1 H, sept), 6.7 (1 H, s), 6.7–7.6 (10 H, m); MS $C_{23}H_{25}FN_2O$ m/e = 364 (M^+), 272, 230. Anal. ($C_{23}H_{25}FN_2O$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxanilide (24f): yield 52%; mp 215–216 °C (not recryst); NMR δ 0.9–2.2 (16 H, d + m), 3.5–4.3 (2 H, m), 6.65 (1 H, s), 6.8–7.6 (10 H, m) MS $C_{26}H_{29}FN_2O$ CI m/e = 405 (M + H^+), 312, 230. Anal. ($C_{26}H_{29}FN_2O$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole-3-carboxanilide (24g): yield 80%; mp 190–192 °C (from cyclohexane/ethyl acetate); NMR δ 1.3 (6 H, d), 1.83 (3 H, s), 3.2 (1 H, sept), 6.8–7.6 (15 H, m); MS $C_{27}H_{25}FN_2O$ m/e = 412 (M^+), 320 (M^+ - PhNH). Anal. ($C_{27}H_{25}FN_2O$) C, H, F, N.

Preparation of Substituted 1*H*-Pyrrole-3-carboxaldehydes 4 from Substituted 1*H*-Pyrrole-3-carboxanilides 24. General Procedure. (a) N-Methylation. To a mechanically stirred solution of anilide **24** (55 mmol) in toluene (300 mL) was added a 50% dispersion of NaH in mineral oil (5.5 g, 115 mmol) at 25 °C under a nitrogen atmosphere. The suspension was warmed for 30 min at 60 °C and for 10 min at 100 °C. The suspension was cooled to 20 °C and methyl iodide (62.5 g, 440 mmol) was added. It was refluxed (bath at 75 °C) for 4–16 h, depending on steric hindrance (TLC control). With external cooling with dry ice/methanol, first water (80 mL) was added dropwise, followed by ether (400 mL). The organic phase was separated, washed with brine, dried, and concentrated in vacuo. The residues often crystallized when swirled with *n*-hexane or diisopropyl ether to a colorless to pale yellow solid. Oily products were purified by chromatography with cyclohexane/ethyl acetate/triethylamine (8:2:0.01) over silica.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 94%; mp 126–127 °C (not recryst); MS $C_{27}H_{25}FN_2O$ m/e = 412 (M^+), 306, 262. Anal. ($C_{27}H_{25}FN_2O$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 73%; oil; NMR δ 1.40 (12 H, d), 3.23 (4 H, s + sept), 4.40 (1 H, sept), 6.50 (1 H, s), 6.5–7.5 (9 H, m); MS $C_{24}H_{27}FN_2O$ m/e = 378 (M^+), 272, 91. Anal. ($C_{24}H_{27}FN_2O$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 98%; mp 102–105 °C (not recryst); NMR δ 1.35 (3 H, d), 1.50 (3 H, d), 1.1–2.2 (11 H, m), 3.25 (3 H, br s) 3.95 (1 H, m), 6.4–7.4 (10 H, m); MS $C_{27}H_{31}FN_2O$ CI m/e = 419 (M + H^+), 312. Anal. ($C_{27}H_{31}FN_2O$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-*N*-methyl-1*H*-pyrrole-3-carboxanilide: yield 84%; mp 62–63 °C (not recryst); NMR δ 1.2 (3 H, d), 1.3 (3 H, d), 1.8 (3 H, s), 2.8 (1 H, sept), 3.17 (3 H, s), 6.5–7.5 (14 H, m); MS $C_{28}H_{27}FN_2O$ m/e = 426 (M^+), 320 (M^+ - $PhNCH_3$). Anal. ($C_{28}H_{27}FN_2O$) C, H, F, N.

(b) Reduction. To a suspension of lithium aluminum hydride (60 mmol) in dry THF (120 mL) under nitrogen was added dropwise a solution of *N*-methylanilides (29 mmol) in THF (120 mL). The mixture was refluxed for 20 h and then cooled to 0 °C. Ethyl acetate (15 mL) and then water (5 mL) followed by 2 N sodium hydroxide solution (10 mL) were added dropwise. The mixture was stirred for 30 min at 25 °C. The solids were removed and washed with ether.

The filtrate was concentrated in vacuo. The residues often crystallized when swirled with *n*-pentane. Oily products were purified by chromatography with toluene/ethyl acetate/triethylamine (20:1:0.01) over silica.

1-Phenyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 92%; oil; NMR δ 1.28 (7 H, d + m), 3.03 (1 H, sept), 4.70 (2 H, s), 6.73 (1 H, s), 6.90–7.70 (9 H, m); MS $C_{20}H_{20}FNO$ m/e = 309 (M^+), 294, 276. Anal. ($C_{20}H_{20}FNO$) C, H, F, N.

1,2-Diisopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 75%; pale yellow oil that slowly crystallized; NMR δ 1.2–1.6 (12 H, m), 2.35 (1 H, br s), 3.33 (1 H, sept), 4.40 (2 H, s), 4.50 (1 H, sept), 6.70 (1 H, s), 6.8–7.65 (4 H, m); MS $C_{17}H_{22}FNO$ CI m/e = 275 (M^+), 258, 242, 200. Anal. ($C_{17}H_{22}FNO$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole: yield 67%; mp 114–116 °C (not recryst); NMR δ 1.37 (6 H, d), 1.2–2.1 (10 H, m), 3.30 (1 H, sept), 3.96 (1 H, m), 4.38 (2 H, s), 6.70 (1 H, s), 6.95 (2 H, m), 7.47 (2 H, m); MS $C_{20}H_{26}FNO$ m/e = 315 (M^+), 300, 282, 200. Anal. ($C_{20}H_{26}FNO$) C, H, F, N.

1-Phenyl-2-isopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole: yield 63%; colorless solid; NMR δ 1.25 (6 H, d), 1.9 (3 H, s), 2.8 (1 H, m), 4.35 (1 H, s), 4.55 (2 H, s), 6.85–7.75 (9 H, m); MS $C_{21}H_{22}FNO$ m/e = 323 (M^+), 308 (M^+ - CH_3), 290 (M^+ - CH_3 - H_2O). Anal. ($C_{21}H_{22}FNO$) C, H, F, N.

(c) Oxidation. Variant A. To a mechanically stirred suspension of Celite (50 g) and finely powdered CrO_3 (25 g, 250 mmol) in dry dichloromethane (250 mL) at 15 °C was added dropwise a solution of dry pyridine (39.5 g, 500 mmol) in CH_2Cl_2 (250 mL).

After stirring at room temperature (20 min), a solution of the substituted (hydroxymethyl)pyrrole (25 mmol) in CH_2Cl_2 (250 mL) was added dropwise but quickly. The reaction temperature was kept between 20 and 24 °C. After 15 min cyclohexane (500 mL) was added. The solid was suction filtered and washed with dichloromethane/cyclohexane (3:7). The filtrate was concentrated and chromatographed with cyclohexane/ethyl acetate/triethylamine (4:1:0.01) over 500 g of silica.

Variant B.[11] To a solution of *N*-methylmorpholine *N*-oxide (46.8 g, 400 mmol) in acetone (400 mL, dried over K_2CO_3) was added tris(triphenylphosphine)ruthenium(II) dichloride (3.8 g, 4.0 mmol). The mixture was stirred 20 min at 20 °C. A solution of the substituted (hydroxymethyl)pyrrole (100 mmol) in dry acetone (600 mL) was added dropwise. The mixture was stirred for 10–20 h at room temperature. After complete reaction (TLC, cyclohexane/ethyl acetate/triethylamine 4:1:0.1), the mixture was filtered through a short, thick silica pad. The pad was washed with ether (3 L); the filtrate was concentrated in vacuo. The residue, pure 4, usually crystallized, when digerated with *n*-pentane at 0 °C.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4b): yield (variant A) 35%, (variant B) 87%; pale yellow solid; mp 119–120 °C; NMR δ 1.36 (6 H, d), 3.16 (1 H, sept), 6.65 (1 H, s), 7.0–7.7 (9 H, m), 10.1 (1 H, s); MS $C_{20}H_{18}FNO$ m/e = 307 (M^+), 292. Anal. ($C_{20}H_{18}FNO$) C, H, F, N.

1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4e): yield (variant B) 87%; yellow oil; NMR δ 1.43 (6 H, d), 1.47 (6 H, d), 3.80 (1 H, sept), 4.57 (1 H, sept), 6.62 (1 H, s), 7.06 (2 H, m), 7.37 (2 H, m), 9.89 (1 H, s); MS $C_{17}H_{20}FNO$ m/e = 273 (M^+), 258, 244. Anal. ($C_{17}H_{20}FNO$) C, H, F, N.

1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4f): yield (variant B) 98%; colorless crystals; mp 134–135 °C; NMR δ 1.45 (6 H, d), 1.1–2.2 (10 H, m), 3.55–4.35 (2 H, m + sept), 6.65 (1 H, s), 6.9–7.6 (4 H, m), 9.95 (1 H, s); MS $C_{20}H_{24}FNO$ m/e = 313 (M^+), 298, 231, 216. Anal. ($C_{20}H_{24}FNO$) C, H, F, N.

1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrole-3-carboxaldehyde (4g): yield (variant A) 45%; pale yellow solid; NMR δ 1.3 (6 H, d), 2.1 (3 H, s), 3.1 (1 H, sept), 6.9–7.6 (9 H, m), 10.0 (1 H, s); MS $C_{21}H_{20}FNO$ m/e = 321 (M^+). Anal. ($C_{21}H_{20}FNO$) C, H, F, N.

Synthesis of 1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxaldehyde (4e) via Three-Component Coupling Reaction According to Scheme VI. (a) Three-Component Coupling. Ethyl 1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrole-3-carboxylate (21e). To a suspension of 4-fluoro-β-nitrostyrene[19] (209 g, 1.25 mol) in absolute methanol (500 mL) was added ethyl 3-oxo-4-methylpentanoate[9] (214 g, 1.35 mol) under ice cooling followed by isopropylamine (128 mL, 1.50 mol), both in one portion. Absolute methanol (1 L) was added, the ice bath was removed, and the reaction mixture was stirred for 48 h in a tightly stoppered flask. Volatile components were removed in vacuo. The brown, viscous oil was filtered with toluene/0.1% triethylamine through 5 kg of silica gel (70–200 μm) to give 197 g (49.7% yield) of a yellow solid: mp 72–74 °C; NMR (CD_2Cl_2) δ 1.07 (3 H, t), 1.36 (6 H, d), 1.42 (6 H, d), 3.73 (1 H, sept), 4.06 (2 H, q), 4.50 (1 H, sept), 6.60 (1 H, s), 6.80–7.40 (4 H, m); MS (DCI, posit, isobutane) $C_{19}H_{24}FNO_2$ m/e = 318 ($M + H^+$), 317, 302. Anal. ($C_{19}H_{24}FNO_2$) C, H, F, N.

(b) Reduction. 1,2-Diisopropyl-3-(hydroxymethyl)-4-(4-fluorophenyl)-1*H*-pyrrole. A solution of the ethyl ester (197 g, 0.62 mol) in ether (750 mL) was added dropwise at 0 °C to a suspension of lithium aluminum hydride (47.2 g, 1.24 mol) in ether (1.5 L). The reaction mixture was stirred for 1 h at 0 °C and for 1 h at 20 °C. At 0–10 °C ethyl acetate (150 mL) was added dropwise, and then water (38 mL) followed by 2 N sodium hydroxide solution (75 mL) was added. The mixture was stirred for 15 min at room temperature. The inorganic solids were removed by suction filtration and washed thoroughly with ether.

Triethylamine (1 mL) was added to the combined filtrate and washings and the solvent was removed in vacuo to give a yellow solid (131 g, 77% yield) that had spectra identical with those of the authentic material described above.

(c) Oxidation was performed as described above to give 4e as a yellow solid in 92% yield.

Pyrrole-Substituted Acrylonitriles 5. General Procedure. At 0 °C a solution of diisopropyl (cyanomethyl)phosphonate (13.5 g, 66.0 mmol) in dry THF (200 mL) was added dropwise to a suspension of sodium hydride (3.78 g of a 50% dispersion in mineral oil, 78.7 mmol) in dry THF (700 mL). After 40 min at 0 °C, a solution of aldehyde 4 (44.0 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 2 h at room temperature. The reaction mixture was poured into 1 L of brine. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic phases were dried and concentrated in vacuo. The residue was chromatographed over silica with cyclohexane/ethyl acetate (6:1), containing 0.1% triethylamine.

β-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5a): yield 78%; pale yellow solid; NMR δ 2.30 (3 H, s), 5.23 (1 H, d), 6.73 (1 H, s), 7.0–7.6 (10 H, m); MS $C_{20}H_{15}FN_2$ m/e = 302 (M^+). Anal. ($C_{20}H_{15}FN_2$) C, H, F, N.

β-[1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5e): yield 91%; crystals; mp 121–123 °C (not recryst); NMR δ 1.43 (12 H, 2 × d), 3.30 (1 H, sept), 4.50 (1 H, sept), 4.93 (1 H, d), 6.60 (1 H, s), 6.9–7.4 (4 H, m), 7.53 (1 H, d); MS $C_{19}H_{21}FN_2$ m/e = 296 (M^+), 281, 256, 239. Anal. ($C_{19}H_{21}FN_2$) C, H, F, N.

β-[1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-acrylonitrile (5f): yield 96%; pale yellow solid; mp 130–132 °C (not recryst); NMR δ 1.40 (6 H, d), 1.2–2.1 (10 H, m), 3.30 (1 H, sept), 4.00 (1 H, m), 4.95 (1 H, d), 6.60 (1 H, s), 6.9–7.4 (4 H, m), 7.55 (1 H, d); MS $C_{22}H_{25}FN_2$ m/e = 336 (M^+), 321, 239. Anal. ($C_{22}H_{25}FN_2$) C, H, F, N.

Preparation of Pyrrole-Substituted Acroleins 6 from Acrylonitriles 5. General Procedure. To a solution of nitrile 5 (24 mmol) in dry THF (200 mL) was added dropwise 60 mL (72 mmol) of a 1.2 M solution of diisobutylaluminum hydride in toluene at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 1.5 h at room temperature. At 0 °C, saturated aqueous sodium dihydrogen phosphate solution (100 mL) and then water (200 mL) were added dropwise. The mixture was stirred for 1 h at room temperature and then saturated with sodium chloride and extracted with ether. The combined organic phases were washed with saturated aqueous sodium bicarbonate and then dried and concentrated in vacuo. The residue was chromatographed over silica with cyclohexane/ethyl acetate (5:1), containing 0.1% triethylamine.

3-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6a): yield 70%; pale yellow solid; NMR δ 2.36 (3 H, s), 6.26 (1 H, dd), 6.97 (1 H, d), 7.15–7.70 (10 H, m), 9.54 (d, 1 H); MS $C_{20}H_{16}FNO$ m/e = 305 (M^+), 290, 276, 264. Anal. ($C_{20}H_{16}FNO$) C, H, F, N.

3-[1,2-Diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6e): yield 70%; crystals; mp 119–121 °C; NMR δ 1.45 (12 H, 2 × d), 3.45 (1 H, sept), 4.53 (1 H, sept), 6.00 (1 H, d), 6.65 (1 H, s), 6.9–7.5 (4 H, m), 7.63 (1 H, d), 9.45 (1 H, d); MS $C_{19}H_{22}FNO$ m/e = 299 (M^+), 256, 214. Anal. ($C_{19}H_{22}FNO$) C, H, F, N.

3-[1-Cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6f): yield 81%; pale yellow crystals; mp 124 °C (not recryst); NMR δ 1.46 (6 H, d), 1.3–2.2 (10 H, m), 3.50 (1 H, sept), 4.00 (1 H, m), 6.05 (1 H, dd), 6.65 (1 H, s), 6.9–7.5 (4 H, m), 7.65 (1 H, d), 9.50 (1 H, d); MS $C_{22}H_{26}FNO$ m/e = 339 (M^+), 296, 214. Anal. ($C_{22}H_{26}FNO$) C, H, F, N.

Synthesis of Pyrrole-Substituted Acroleins 6 from Aldehydes 4 with the Wollenberg Reagent. General Procedure. To a solution of 1-ethoxy-2-(tri-*n*-butylstannyl)ethylene[20] (3.46 g, 9.6 mmol) in dry THF (110 mL) was added a solution of *n*-butyllithium in *n*-hexane (6.25 mL of a 1.6 M solution, 10 mmol) at −70 °C under nitrogen. After 2 h at −73 °C, a solution of the aldehyde 4 (8 mmol) in THF (12 mL) was added dropwise. During this operation, the reaction temperature rose to −66 °C. After 2 h at −73 °C and 10 min at −50 °C, a saturated aqueous ammonium chloride solution (18.6 mL) was added dropwise at −40 °C. The mixture was allowed to warm to room temperature. The organic layer was separated; the aqueous layer was extracted twice

(20) Leusink, A. J.; Budding, H. A.; Drenth, W. *J. Organomet. Chem.* **1967**, *9*, 285.

with ether. The combined organic layers were washed with brine and then dried and concentrated in vacuo. The residue was taken up in THF (93 mL) and water containing *p*-toluenesulfonic acid (18 mL) and stirred for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and then dried and concentrated. The residue was chromatographed with cyclohexane/ethyl acetate/triethylamine (3:1:0.1) over 450 g of silica.

3-[1-Phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6a): yield 98%; spectra, see above.

3-[1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6b): yield 50% (46% recovered starting material); NMR δ 1.35 (6 H, d), 3.16 (1 H, sept), 6.05 (1 H, dd), 6.63 (1 H, s), 7.0–7.5 (9 H, m), 7.75 (1 H, d), 9.50 (1 H, d); MS $C_{22}H_{20}FNO$ DCI m/e = 334 ($M + H^+$), 290. Anal. ($C_{22}H_{20}FNO$) C, H, F, N.

3-[1-Phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6c): yield 88%; amorphous solid; NMR δ 1.9 (3 H, s), 2.2 (3 H, s), 6.07 (1 H, dd), 6.9–7.7 (10 H, m), 9.45 (1 H, d); MS $C_{21}H_{18}FNO$ m/e = 319 (M^+), 290 ($M^+ - CHO$). Anal. ($C_{21}H_{18}FNO$) C, H, F, N.

3-[1-Isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-(*E*)-propenal (6d): yield 94%; colorless solid; NMR δ 1.47 (6 H, d), 2.43 (3 H, s), 4.42 (1 H, sept), 6.20 (1 H, dd), 6.72 (1 H, s), 6.9–7.5 (4 H, m), 7.50 (1 H, d), 9.48 (1 H, d); MS $C_{17}H_{18}FNO$ m/e = 271 (M^+), 256, 242, 200. Anal. ($C_{17}H_{18}FNO$) C, H, F, N.

3-[1-Phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]-(*E*)-propenal (6g): yield 91%; yellow solid; NMR δ 1.3 (6 H, d), 2.0 (3 H, s), 3.1 (1 H, sept), 6.1 (1 H, dd), 7.0–7.8 (10 H, m), 9.5 (1 H, d); MS $C_{23}H_{22}FNO$ DCI m/e = 348 ($M + H^+$). Anal. ($C_{23}H_{22}FNO$) C, H, F, N.

β-Keto-δ-hydroxy Esters 7. General Procedure. To a suspension of sodium hydride (12.7 mmol) in THF (86 mL) was added dropwise a solution of methyl acetoacetate (1.43 g, 12.33 mmol) in THF (10 mL) at −15 °C during 5 min. The solution was stirred for 50 min at −15 °C. A solution of *n*-butyllithium in hexane (7.68 mL of a 1.6 M solution, 12.26 mmol) was added during 10 min. The reaction mixture was stirred for 20 min at −15 °C. A solution of aldehyde **6** (7.0 mmol) in THF (25 mL) was added during 10 min. The reaction mixture was stirred for 45 min at −15 °C. At −10 °C, a saturated sodium dihydrogen phosphate solution (13 mL) was added dropwise. After 5 min at 0 °C, the mixture was distributed between ether and brine. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, concentrated, and chromatographed with cyclohexane/ethyl acetate/triethylamine (2:1:0.1) over silica, giving a pale yellow oil (76–85% yield).

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7a): NMR δ 2.27 (3 H, s), 2.55 (1 H, br), 2.80 (2 H, m), 3.50 (2 H, s), 3.74 (3 H, s), 4.69 (1 H, q), 5.65 (1 H, dd), 6.60 (1 H, d), 6.76 (1 H, s), 7.00–7.12 (4 H, m), 7.30–7.52 (5 H, m); MS $C_{25}H_{24}FNO_4$ m/e = 421 (M^+), 403, 345, 302. Anal. ($C_{25}H_{24}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7b): MS $C_{27}H_{28}FNO_4$ m/e = 449 (M^+), 432, 373, 334, 290. Anal. ($C_{27}H_{28}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7c): NMR δ 1.6 (1 H, s), 1.9 (3 H, s), 2.13 (3 H, s), 2.36 (2 H, s), 3.57 (2 H, AB), 3.73 (3 H, s), 5.99 (1 H, d), 6.16 (1 H, dd), 6.94 (1 H, d), 7.08–7.33 (5 H, m), 7.44–7.58 (4 H, m); MS $C_{26}H_{26}FNO_4$ m/e = 435 (M^+), 417, 320, 319. 316, 290. Anal. ($C_{26}H_{26}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7d): NMR δ 1.44 (8 H, d + m), 1.58 (1 H, br s), 2.37 (3 H, s), 3.58 (2 H, s), 3.75 (3 H, s), 4.35 (1 H, sept), 6.02 (1 H, d), 6.27 (1 H, dd), 6.67 (1 H, s), 7.06 (2 H, m), 7.28 (2 H, m); MS $C_{22}H_{26}FNO_4$ m/e = 387 (M^+), 369, 272. Anal. ($C_{22}H_{26}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7e): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.42 (6 H, d), 2.37 (1 H, d), 2.68 (2 H, m), 3.30 (1 H, sept), 3.48 (2 H, s), 3.70 (3 H, s), 4.44 (1 H, sept), 4.59 (1 H, m), 5.32 (1 H, dd), 6.62 (1 H, d), 7.00 (2 H, m), 7.30 (2 H, m); MS $C_{24}H_{30}FNO_4$ m/e = 415 (M^+), 397, 300, 256. Anal. ($C_{24}H_{30}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7f): NMR (CD_2Cl_2) δ 1.35 (6 H, d), 1.3–2.3 (10 H, m), 2.35 (1 H, d), 2.65 (2 H, d), 3.30 (1 H, sept), 3.50 (2 H, s), 3.70 (3 H, s), 4.00 (1 H, m), 4.60 (1 H, m), 5.35 (1 H, dd), 6.65 (1 H, s), 6.65 (1 H, d), 6.85–7.50 (4 H, m); MS $C_{27}H_{34}FNO_4$ m/e = 455 (M^+), 437, 340, 296, 214. Anal. ($C_{27}H_{34}FNO_4$) C, H, F, N.

Methyl 5(*RS*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (7g): MS $C_{28}H_{30}FNO_4$ m/e = 463 (M^+), 446. Anal. ($C_{28}H_{30}FNO_4$) C, H, F, N.

β,δ-Dihydroxy Esters 1 ($R^1 = CH_3$). General Procedure. To a solution of β-keto-δ-hydroxy ester **7** (5 mmol) in dry THF (70 mL) was added dropwise a solution of triethylborane in THF (6 mL of a 1 M solution, 6 mmol) during 5 min. After 20 min at 20 °C, 14 mL of dry air was bubbled through the solution with a syringe. After 2 h at 20 °C, the reaction mixture was cooled to −75 °C. Sodium borohydride (246 mg, 6.5 mmol) was added at once. After 12 h at −75 °C under nitrogen, the mixture was allowed to warm to −10 °C and saturated sodium dihydrogen phosphate solution (35 mL) was added dropwise. The reaction mixture was partitioned between ether and brine. The organic layer was washed with brine, dried, and concentrated. The residue was stirred for 3 h with dry methanol (300 mL). The solvent was evaporated and the residue was chromatographed with cyclohexane/ethyl acetate/triethylamine (1:1:0.1) through silica to yield 60–85% of a thick, pale yellow oil.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1a): NMR δ 2.12 (2 H, m), 2.24 (3 H, s), 2.37 (2 H, s), 2.54 (1 H, dd), 2.75 (1 H, dd), 3.72 (3 H, s), 4.26 (1 H, m), 5.32 (1 H, m), 5.75–5.85 (2 H, m), 6.78 (1 H, s), 7.00–7.10 (2 H, m), 7.28–7.50 (7 H, m); MS $C_{25}H_{26}FNO_4$ m/e = 423 (M^+), 306, 264. Anal. ($C_{25}H_{26}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1b): NMR (C_6D_6) δ 1.30 (7 H, d + m), 1.57 (1 H, dt), 2.03 (1 H, dd), 2.18 (1 H, dd), 2.70 (1 H, br s), 3.09 (1 H, sept), 3.27 (3 H, s), 3.45 (1 H, br s), 4.03 (1 H, m), 4.34 (1 H, m), 5.67 (1 H, dd), 6.50 (1 H, s), 6.87–7.15 (8 H, m), 7.45 (2 H, dd); MS $C_{27}H_{30}FNO_4$ m/e = 451 (M^+), 433, 334, 292, 290, 276. Anal. ($C_{27}H_{30}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1c): NMR (C_6D_6) δ 1.37 (1 H, dt), 1.67 (1 H, dt), 1.90 (3 H, s), 2.08 (3 H, s), 2.05–2.12 (1 H, dd), 2.26 (1 H, dd), 2.40 (1 H, d), 3.26 (3 H, s), 3.48 (1 H, d), 4.11 (1 H, m), 4.30 (1 H, m), 5.72 (1 H, dd), 6.72 (1 H, d), 6.85–6.91 (2 H, m), 6.95–7.17 (5 H, m), 7.32–7.40 (2 H, m); MS $C_{26}H_{28}FNO_4$ m/e = 437 (M^+), 419, 320, 302, 278. Anal. ($C_{26}H_{28}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1d): NMR (C_6D_6) δ 0.98 (6 H, d), 1.40 (1 H, dt), 1.68 (1 H, dt), 2.05 (3 H, s), 2.09 (1 H, dd), 2.27 (1 H, dd), 3.27 (3 H, s), 3.73 (1 H, sept), 4.14 (1 H, m), 4.34 (1 H, m), 5.72 (1 H, dd), 6.50 (1 H, s), 6.73 (1 H, d), 6.98 (2 H, m), 7.43 (2 H, m); MS $C_{22}H_{28}FNO_4$ m/e = 389 (M^+), 272, 230. Anal. ($C_{22}H_{28}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1e): NMR (CD_2Cl_2) δ 1.35 (6 H, d), 1.42 (6 H, d), 1.50–1.70 (2 H, m), 2.45 (2 H, d), 2.62 (1 H, br s), 3.31 (1 H, sept), 3.54 (1 H, d), 3.68 (3 H, s), 4.22 (1 H, m), 4.33–4.52 (2 H, sept + m), 5.32 (1 H, d), 6.58 (1 H, d), 6.62 (1 H, s), 7.00 (2 H, m), 7.31 (2 H, m); MS $C_{24}H_{32}FNO_4$ m/e = 417 (M^+), 399 ($M^+ - H_2O$), 300, 258, 212. Anal. ($C_{24}H_{32}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1f): NMR (CD_2Cl_2) δ 1.25–2.05 (12 H, m), 1.34 (6 H, d), 2.45 (2 H, d), 2.62 (1 H, d), 3.30 (1 H, sept), 3.55 (1 H, d), 3.69 (3 H, s), 3.95 (1 H, tt), 4.20 (1 H, m), 4.38 (1 H, m), 5.33 (1 H, dd), 6.58 (1 H, d), 6.62 (1 H, s), 7.00 (2 H, m), 7.30 (2 H, m); MS $C_{27}H_{36}FNO_4$ m/e = 457 (M^+), 439 ($M^+ - H_2O$), 421 ($M^+ - 2H_2O$), 366, 340, 298, 212. Anal. ($C_{27}H_{36}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1g): NMR (C_6D_6) δ 1.3 (7 H, d + m), 1.6 (1 H, m), 1.95 (3 H, s), 2.0–2.3 (2 H, m), 2.5 (1 H, br s), 3.1 (1 H, sept), 3.3 (3 H, s), 3.5 (1 H, s), 4.1 (1 H, m), 4.3 (1 H, m), 5.7 (1 H, dd), 6.8–7.5 (10 H, m); MS $C_{28}H_{32}FNO_4$ m/e = 465 (M^+), 447 ($M^+ - H_2O$). Anal. ($C_{28}H_{32}FNO_4$) C, H, F, N.

Hydrogenated β,δ-Dihydroxy Esters 2 ($R^1 = CH_3$). General Procedure. Ten percent palladium on charcoal (2.2 g) was added under nitrogen to a solution of the olefinic β,δ-dihydroxy ester 1 ($R^1 = CH_3$) (70 mmol) in methanol (1.3 L) and triethylamine (13 mL). The mixture was shaken for 20 min in a hydrogen atmosphere at atmospheric pressure and room temperature. H_2 (1240 mL) was taken up (theoretical 1570 mL). The catalyst was filtered off and washed with methanol. The filtrate was concentrated in vacuo. The residue was chromatographed with cyclohexane/ethyl acetate (5:3), containing 0.1% triethylamine, through 1.3 kg of silica. The first compound eluted was the pure product 2 (yield 75–80%, pale yellow thick oil). Shortly thereafter a diastereomer of 2 (yield 8%) was eluted that stemmed either from incomplete stereoselectivity during the borane-catalyzed reduction of keto ester 6 (steps i, j) or from some isomerization during the catalytic hydrogenation. As a last fraction, the lactonized form of 2 (yield 4–5%) was obtained, containing some diastereomers. TLC (cyclohexane/ethyl acetate 1:1, silica) R_f values: 1 (starting material), 0.26; 2, 0.29; diastereomer of 2, 0.25; δ-lactone of 2, 0.19.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2b): NMR (C_6D_6) δ 1.03 (1 H, dt), 1.28–1.43 (1 H, m), 1.32 (3 H, d), 1.33 (3 H, d), 1.60–1.85 (2 H, m), 1.94 (1 H, dd), 2.12 (1 H, dd), 2.90–3.02 (1 H, m), 3.03–3.22 (3 H, m), 3.24 (3 H, s), 3.43 (1 H, br s), 3.75 (1 H, m), 3.88 (1 H, m), 6.58 (1 H, s), 6.94 (2 H, m), 7.03–7.15 (5 H, m), 7.42 (2 H, m); MS $C_{27}H_{32}FNO_4$ FAB m/e = 454 (M + H^+), 292. Anal. ($C_{27}H_{32}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2,5-dimethyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2c): NMR (C_6D_6) δ 1.10 (1 H, dt), 1.38 (1 H, dt), 1.50–1.76 (2 H, m), 1.97 (3 H, s), 2.01 (1 H, dd), 2.08 (3 H, s), 2.17 (1 H, dd), 2.77 (2 H, m), 2.86 (1 H, d), 3.27 (3 H, s), 3.50 (1 H, d), 3.72 (1 H, m), 3.95 (1 H, m), 6.90–7.13 (7 H, m), 7.28–7.36 (2 H, m); MS $C_{26}H_{30}FNO_4$ m/e = 439 (M^+), 407, 279. Anal. ($C_{26}H_{30}FN$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-isopropyl-2-methyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2d): NMR (C_6D_6) δ 1.02 (6 H, 2 × d), 1.38 (2 H, dt), 1.50–1.75 (2 H, m), 1.97 (1 H, dd), 2.10 (3 H, s), 2.15 (1 H, dd), 2.82 (2 H, m), 3.27 (3 H, s), 3.70 (1 H, m), 3.78 (1 H, sept), 3.93 (1 H, m), 6.58 (1 H, s), 6.98 (2 H, m), 7.39 (2 H, m); MS $C_{22}H_{30}FNO_4$ DCI m/e = 392 (M + H^+), 391, 360, 331, 230. Anal. ($C_{22}H_{30}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2e): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.42 (6 H, d), 1.4–1.55 (4 H, m), 2.40 (2 H, d), 2.50–2.76 (2 H, m), 2.87 (1 H, br s), 3.22 (1 H, sept), 3.60 (1 H, br d), 3.68 (3 H, s), 3.76 (1 H, qui), 4.12 (1 H, qui), 4.43 (1 H, sept), 6.62 (1 H, s), 7.03 (2 H, m), 7.32 (2 H, m); MS $C_{24}H_{34}FNO_4$ DCI m/e = 420 (M + H^+), 419 (M^+), 259. Anal. ($C_{24}H_{34}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-cyclohexyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2f): NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.3–1.8 (10 H, m), 1.32–2.05 (4 H, m), 2.39 (2 H, d), 2.50–2.72 (2 H, m), 2.88 (1 H, br s), 3.22 (1 H, sept), 3.61 (1 H, br d), 3.67 (3 H, s), 3.76 (1 H, qui), 3.94 (1 H, tt), 4.12 (1 H, qui), 6.61 (1 H, s), 7.02 (2 H, m), 7.31 (2 H, m); MS $C_{27}H_{38}FNO_4$ m/e = 459 (M^+), 427 ($M^+ - CH_3OH$), 299, 298, 256. Anal. ($C_{27}H_{38}FNO_4$) C, H, F, N.

Methyl 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-3-yl]heptanoate (2g): NMR (C_6D_6) δ 1.1–1.5 (2 H, m), 1.3 (6 H, d), 1.6–2.2 (7 H, m + s), 2.9–3.2 (4 H, m), 3.3 (3 H, s), 3.45 (1 H, br s), 3.8–4.1 (2 H, m), 6.8–7.5 (9 H, m); MS $C_{28}H_{34}FNO_4$ FAB m/e = 468 (M + H^+). Anal. ($C_{28}H_{34}FNO_4$) C, H, F, N.

Optically Active HMG-CoA Reductase Inhibitors of General Formula 13 via Asymmetric Synthesis According to Scheme II. (a) Diastereoselective Aldol Reaction of Enolate 8 with Aldehydes 6. General Procedure. To a solution of diisopropylamine (97 mL, 70.0 g, 692 mmol) in dry THF (500 mL), cooled with dry ice, was added a 1.6 M solution of *n*-butyllithium in hexane (430 mL, 688 mmol) via a Flex-needle.[21] The mixture was stirred for 30 min at 0 °C under nitrogen. Another 4-L-four-necked flask, equipped with a mechanical stirrer, low-temperature thermometer, dropping funnel with cooling finger, and nitrogen inlet/mercury bubbler, was charged with (*S*)-(−)-phenyl 2-hydroxy-2,2-diphenylacetate[7] (104.7 g, 315 mmol) and dry THF (1 L). The suspension was cooled with dry ice.

A LDA-solution (vide supra) was transferred via a Flex-needle through a septum into the dropping funnel and added to the stirred suspension at such a rate that the reaction temperature stayed below −20 °C. The mixture was stirred for 30 min at 0 °C and became a reddish-brown, clear solution. A precooled solution of aldehyde 6 (300 mmol) in dry THF (300 mL) was added to this solution of dianion 8 at −90 °C. The reaction mixture was stirred for 1–2 h (TLC control) at this temperature. The cold mixture was poured into the mechanically stirred saturated aqueous solution of ammonium chloride (2 L) and stirred for 20 min (pH 8, 0 °C). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and filtered, and the solvent was evaporated in vacuo to give a pale yellow solid that according to TLC consisted mostly of aldol product 9 with small amounts of unreacted chiral acetate and traces of unreacted aldehyde 6. For purification, the crude solid was shaken with hot toluene/ethyl acetate (2 L, 6:4 + 0.1% triethylamine). After the suspension had come to room temperature it was filtered, and the solid after washing with toluene was discarded. Combined filtrate and washings were evaporated in vacuo, and the remaining solid residue was stirred with *n*-pentane (2 × 1 L). The resulting suspension was suction filtered. Colorless solid 9, obtained in 95–98% yield, was pure by TLC. The pentane solution contained unreacted aldehyde 6.

The diastereomeric excess (de) of the desired 3*S* isomer of 9 was 95–96% according to HPLC analysis (LiChrosorb SI 60 Merck 506487, 40 °C, 1.2 mL/min *n*-hexane/methyl *tert*-butyl ether 3:1).

(*S*)-(−)-2-Hydroxy-1,2,2-triphenylethyl (3*S*)-hydroxy-5-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]-pent-4(*E*)-enoate (9b): mp 188–190 °C; NMR (CD_2Cl_2) δ 1.22 (6 H, 2 × d), 1.53 (1 H, s), 1.57 (1 H, d), 2.38 (2 H, d), 3.00 (1 H, hept), 4.37 (1 H, m), 5.28 (1 H, dd, J = 16 and 7 Hz), 6.59 (1 H, s), 6.67 (1 H, dd, J = 16 and 1.5 Hz), 6.69 (1 H, s), 6.93–7.58 (24 H, m); MS (DCI, posit, isobutane) $C_{44}H_{40}FNO_4$ m/e = 665 (M^+), 648 (M^+ − OH), 376, 334. Anal. ($C_{44}H_{40}FNO_4$) C, H, F, N.

(*S*)-(−)-2-Hydroxy-1,2,2-triphenylethyl (3*S*)-hydroxy-5-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4-(*E*)-enoate (9e): mp 194 °C; NMR (CD_2Cl_2) δ 1.32 (6 H, d), 1.43 (6 H, d), 2.10 (1 H, d), 2.38 (2 H, d), 2.98 (1 H, s), 3.27 (1 H, sept), 4.37 (1 H, m), 4.43 (1 H, sept), 5.23 (1 H, dd, J = 16 and 7 Hz), 6.53 (1 H, dd, J = 16 and 1.5 Hz), 6.62 (1 H, s), 6.68 (1 H, s), 6.93–7.01 (2 H, m), 7.05–7.37 (15 H, m), 7.50–7.60 (2 H, m); MS (FAB, NBA/LiI) $C_{41}H_{42}FNO_4$ m/e = 638 (M + Li^+), 631 (M^+), 614 (M^+ − OH), 358, 342, 300. Anal. ($C_{41}H_{42}FNO_4$) C, H, F, N.

(b) Transesterification of 9 to Optically Active Methyl Esters 10. General Procedure. To a suspension of ester 9 (178 mmol) in absolute methanol (1.4 L) was added dropwise a solution of sodium (2.0 g, 89 mmol) in absolute methanol (200 mL) at 20 °C. The mixture was stirred for 3 h at room temperature. At <10 °C, the mixture was neutralized by dropwise addition of the solution of acetic acid (5.1 mL, 89 mmol) in methanol (15 mL). Triethylamine (0.5 mL) was added, and the solvent was evaporated

(21) Commercially available from Aldrich Chemical Co., Milwaukee, WI.

(22) The oral activity in the rat is an *acute* experiment, in which the hepatic cholesterol biosynthesis inhibition is measured within 3 h after po administration. Oral activities in the rabbit and dog are *chronic* experiments, in which decrease of serum cholesterol is measured. The decrease of serum cholesterol should be coupled to the hepatic cholesterol biosynthesis inhibition, but only via a long, complex chain of biochemical reactions. It seems possible that pronounced differences of the two compounds in metabolic stability and pharmacokinetics are responsible for the lack of oral activity of the unsaturated compound 1b in the rabbit model.

at <20 °C in vacuo. The solid residue was taken up in ether and half-concentrated brine. The ether phase was washed with sodium bicarbonate and then with brine. The solvent was removed in vacuo. The liberated diol was removed from methyl ester **10** by filtration with diisopropyl ether/cyclohexane (1:1) through 2 kg of silica: yield 94–100% **10**; pale-yellow oil.

Methyl esters **10** decomposed quickly in solution at room temperature, especially on air contact.

Methyl (3*S*)-hydroxy-5-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4(*E*)-enoate (10b): NMR (CD_2Cl_2) δ 1.26 (6 H, d), 2.48 (2 H, AB of AB X), 3.03 (1 H, hept), 3.60–3.71 (1 H, m), 3.67 (3 H, s), 4.53 (1 H, br s), 5.37 (1 H, dd), 6.58 (1 H, s), 6.72 (1 H, dd), 7.00 (2 H, m), 7.27–7.49 (7 H, m). Anal. ($C_{25}H_{26}FNO_3$) C, H, F, N.

Methyl (3*S*)-hydroxy-5-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]pent-4(*E*)-enoate (10e): MS (DCI, posit, isobutane) $C_{22}H_{28}FNO_3$ *m/e* = 373 (M^+), 356 (M^+ – OH). Anal. ($C_{22}H_{28}FNO_3$) C, H, F, N.

(c) Transformation of δ-Hydroxy Methyl Esters 10 to β-Keto-δ-hydroxy *tert*-Butyl Esters 11. General Procedure. *tert*-Butyl acetate (81.3 g, 94 mL, 700 mmol) was added dropwise at –75 °C under N_2 to a solution of LDA (730 mmol) in THF/hexane (1:1, 1 L). After 40 min at –70 °C, the solution of methyl ester **10** (178 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 10 min at –70 °C and then for 1 h at –30 °C. The cold solution was poured into mechanically stirred, half-saturated ammonium chloride solution (2 L). After 10 min, the organic phases were washed twice with sodium bicarbonate solution and then with brine, dried, filtered, and evaporated. Toluene (100 mL) was added and then evaporated at 20 °C (to remove the excess *tert*-butyl acetate). Residual volatile components were removed in high vacuo (24 h). *tert*-Butyl esters **11** were obtained as yellow, very viscous oils in 95–100% yield.

***tert*-Butyl (5*S*)-hydroxy-3-oxo-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (11b)**: NMR (CD_2Cl_2) δ 1.25 (6 H, d), 1.46 (9 H, s), 2.68 (2 H, d), 3.03 (1 H, hept), 3.37 (2 H, s), 3.68 (1 H, m), 4.60 (1 H, m), 5.37 (1 H, dd), 6.60 (1 H, s), 6.74 (1 H, dd), 7.03 (2 H, m), 7.30–7.52 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{34}FNO_4$ *m/e* = 491 (M^+), 474 (M^+ – OH), 418 (M^+ – isobutene), 390 (M^+ – CO_2tBu), 334. Anal. ($C_{30}H_{34}FNO_4$) C, H, F, N.

***tert*-Butyl (5*S*)-hydroxy-3-oxo-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (11e)**: NMR (CD_2Cl_2) δ 1.36 (6 H, d), 1.40–1.48 (15 H, s + 2 × d), 1.57 (1 H, d), 2.67 (2 H, d), 3.32 (1 H, hept), 3.36 (2 H, s), 4.45 (1 H, hept), 4.57 (1 H, m), 5.32 (1 H, dd, *J* = 16 and 7 Hz), 6.62 (1 H, dd, *J* = 16 and 1.5 Hz), 6.63 (1 H, s), 7.00 (2 H, m), 7.30 (2 H, m); MS (DCI, posit, isobutane) $C_{27}H_{36}FNO_4$ *m/e* = 457 (M^+), 440 (M^+ – OH), 397. Anal. ($C_{27}H_{36}FNO_4$) C, H, F, N.

(d) Diastereoselective Reduction of β-Keto-δ-hydroxy *tert*-Butyl Esters 11 to β,δ-Dihydroxy *tert*-Butyl Esters 12. General Procedure. Triethylborane (185 mL of a 1 M solution in THF) was added dropwise at 20 °C to a solution of 130 mL of absolute methanol in 510 mL of dry THF. A solution of crude *tert*-butyl ester **11** (177 mmol) in THF (150 mL) was added dropwise. The mixture was stirred for 1 h at –70 °C. Sodium borohydride (8.73 g, 231 mmol) was added at once. The mixture was stirred for 1.5 h at –70 °C and then poured into half-concentrated ammonium chloride solution (2 L). The mixture was stirred for 15 min and the organic phase was separated. The aqueous phase was extracted twice with ether. The combined organic layers were washed with brine, and the solvent was evaporated in vacuo. The residue was taken up several times in wet methanol and this solvent was evaporated in vacuo at <20 °C. TLC (100% diisopropyl ether) indicated the successful conversion of the unpolar boron ester of the diol (R_f ~0.57) to free diol **12** (R_f ~0.19). Pure **12** was obtained after chromatography through silica (2 kg, 70–200 μm) with diisopropyl ether as a colorless solid (yield 70–80%).

***tert*-Butyl 3(*R*),5(*S*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (12b)**: mp 107–110 °C; NMR (CD_2Cl_2) δ 1.26 (6 H, d), 1.48 (9 H, s). 1.55 (2 H, m), 2.38 (2 H, d), 2.87 (1 H, t), 3.03 (1 H, hept), 3.63 (1 H, br s), 4.16 (1 H, m), 4.39 (1 H, m), 5.37 (1 H, dd), 6.60 (1 H, s), 6.71 (1 H, dd), 7.03 (2 H, m), 7.30–7.52 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{36}FNO_4$ *m/e* = 493 (M^+), 476 (M^+ – OH), 458 (M^+ – OH – H_2O). Anal. ($C_{30}H_{36}FNO_4$) C, H, F, N.

***tert*-Butyl 3(*R*),5(*S*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (12e)**: MS (DCI, posit, isobutane) $C_{27}H_{38}FNO_4$ *m/e* = 459 (M^+). Anal. ($C_{27}H_{38}FNO_4$) C, H, F, N.

(e) Catalytic hydrogenations of *tert*-butyl esters 12 were performed in analogy to that of the corresponding methyl esters **2** (vide supra), yield 75–82%.

***tert*-Butyl 3(*R*),5(*R*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate**: mp 108–110 °C; NMR (CD_2Cl_2) δ 1.25 (6 H, d), 1.46 (9 H, s), 1.40–1.57 (4 H, m), 2.33 (2 H, m), 2.63–2.91 (2 H, m), 3.02 (1 H, hept), 3.13 (1 H, br s), 3.67 (1 H, br s), 3.79 (1 H, qui), 4.11 (1 H, br qui), 6.62 (1 H, s), 7.05 (2 H, m), 7.30–7.50 (7 H, m); MS (DCI, posit, isobutane) $C_{30}H_{38}FNO_4$ 496 (M + H^+), 495 (M^+), 440 (M + H^+ – isobutene), 293. Anal. ($C_{30}H_{38}FNO_4$) C, H, F, N.

***tert*-Butyl 3(*R*),5(*R*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate**: mp 128–130 °C; MS (DCI, posit, isobutane) $C_{27}H_{40}FNO_4$ *m/e* = 462 (M + H^+), 461 (M^+), 406 (M + H^+ – isobutene), 259. Anal. ($C_{27}H_{40}FNO_4$) C, H, F, N.

β,δ-Dihydroxy Sodium Carboxylates 1 or 2 (R^1 = Na). General Procedure. To a solution of methyl ester **1** or **2** (R^1 = CH_3, 48 mmol) in methanol (500 mL) was added dropwise 1 N aqueous sodium hydroxide solution (50 mL, 50 mmol) during 1 h at 0–10 °C. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was taken up in ethanol (100 mL), evaporated in vacuo, and dried in high vacuo. The residue was stirred with ether (300 mL). The solid was collected by suction filtration, washed with pentane, and dried for 4 h in vacuo in a desiccator over phosphorous pentoxide and potassium hydroxide; pale yellow solid, yield 64%. The ethereal mother liquor was evaporated in vacuo and treated as described above to give a solid with the same melting point and ^1H NMR; yield 31%, combined yield 95%.

Sodium 3(*RS*),5(*SR*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]hept-6(*E*)-enoate (1b): mp 232–234 °C dec; NMR (DMSO-d_6) δ 1.20 (6 H, d), 1.25–1.62 (2 H, m), 1.80–2.11 (2 H, m), 2.98 (1 H, sept), 3.72 (1 H, m), 4.20 (1 H, m), 4.83 (1 H, br s), 5.37 (1 H, dd), 6.52 (1 H, d), 6.80 (1 H, s), 7.14 (2 H, t), 7.30 (1 H, br s), 7.40–7.60 (8 H, m). Anal. ($C_{26}H_{27}FNO_4Na$) C, H, N.

Sodium 3(*RS*),5(*RS*)-dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (2b): mp 231–233 °C dec. Anal. ($C_{26}H_{29}FNO_4Na$) C, H, N.

Sodium 3(*R*),5(*R*)-Dihydroxy-7-[1-phenyl-2-isopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (13b). The corresponding *tert*-butyl ester (48 g, 97 mmol) was suspended in ethanol (250 mL) at 5 °C. Sodium hydroxide (1 N, 98.8 mL) was added dropwise. The suspension was stirred for 20 h at room temperature, becoming a clear solution. Solvents were removed in vacuo. The residue was washed with ether and then with pentane to give 44.6 g (yield 99.8%) of a colorless solid: mp 252–254 °C dec; NMR (DMSO-d_6) δ 1.22 (6 H, d), 1.20–1.50 (4 H, m), 1.83 (1 H, dd, *J* = 15 and 8 Hz), 2.04 (1 H, dd, *J* = 15 and 4 Hz), 2.50–2.67 (1 H, m), 2.71–2.87 (1 H, m), 2.96 (1 H, hept), 3.61 (1 H, br s), 3.74 (1 H, m), 4.70 (1 H, br s), 6.77 (1 H, s), 7.10–7.21 (2 H, m), 7.32–7.57 (7 H, m). Anal. ($C_{26}H_{29}FNO_4Na$) C, H, N.

Sodium 3(*R*),5(*R*)-dihydroxy-7-[1,2-diisopropyl-4-(4-fluorophenyl)-1*H*-pyrrol-3-yl]heptanoate (13e) was obtained from the corresponding *tert*-butyl ester in analogy to the method for **13b** (vide supra) to give a colorless solid: mp 255 °C dec; NMR (DMSO-d_6) δ 1.30 (6 H, d), 1.37 (6 H, d), 1.82 (1 H, dd, *J* = 15 and 8 Hz), 2.03 (1 H, dd, *J* = 15 and 4 Hz), 2.32–2.48 (1 H, m), 2.52–2.67 (1 H, m), 3.18 (1 H, hept), 3.57 (1 H, br s), 3.76 (1 H, hept), 4.41 (1 H, hept), 4.57 (1 H, br s), 6.80 (1 H, s), 7.12 (2 H, m), 7.33 (2 H, m). Anal. ($C_{23}H_{31}FNO_4Na$) C, H, N.

Biological assays: see the preceding paper in this issue.