PERKIN 1

Synthesis and reactions of Biginelli-compounds. Part 23.[1] Chemoenzymatic syntheses of enantiomerically pure 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones

Barbara Schnell, Wolfram Krenn, Kurt Faber and C. Oliver Kappe*

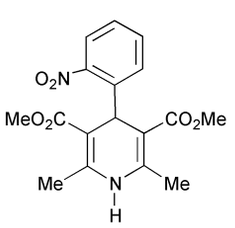
Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Received (in Cambridge, UK) 3rd August 2000, Accepted 1st November 2000
First published as an Advance Article on the web 30th November 2000

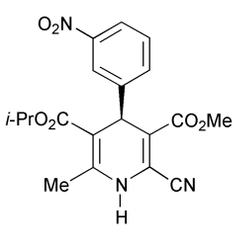
Enantiomerically pure dihydropyrimidones (DHPMs) were prepared by lipase-catalyzed enzymatic resolution of two types of activated DHPM esters. In the first model series, pivaloyloxymethyl-activated DHPM C5-esters **10a**–**c** were resolved on an analytical scale by various lipases in two different solvent systems with selectivities $E < 50$. Alternatively, attachment of an acetoxymethyl residue at the N3 position of the DHPM scaffold led to activated ester **15**, which was selectively cleaved by *Thermomyces lanuginosus* lipase ($E > 200$) to furnish, after deprotection, DHPMs (*R*)- and (*S*)-**13** on a semi-preparative scale. Treatment of (*R*)-**13** with trichloroacetyl isocyanate produced the antihypertensive agent (*R*)-SQ 32926.

Introduction

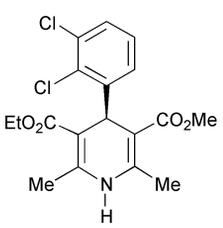
4-Aryl-1,4-dihydropyridines of the nifedipine type (DHPs, *e.g.* **1**–**3**) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.[2] More than 25 years after the introduction of nifedipine (**1**), many DHP analogs have been synthesized and numerous second-generation commercial products have appeared on the market.[3] In contrast to the achiral nifedipine (**1**), different substituents in these compounds led to chiral derivatives possessing an asymmetric carbon at the C4-position (*e.g.* **2**, **3**). The fact that there is a difference in pharmacological activity (calcium entry blocking *versus* activating) between individual DHP enantiomers has been reported by several groups.[4]



1, nifedipine

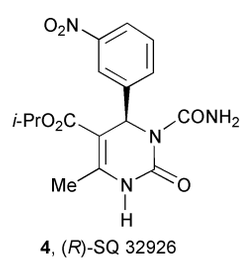


2, (*R*)-nilvadipine

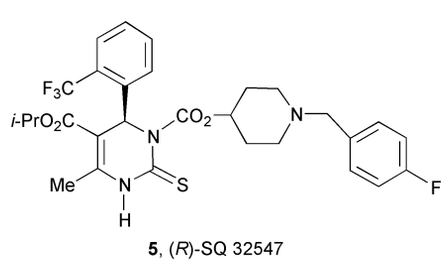


3, (*S*)-felodipine

In recent years, interest has also focused on aza-analogs such as dihydropyrimidones of type **4** and **5** (DHPMs) which show a very similar pharmacological profile to classical DHP calcium channel modulators.[5–7] The DHPM scaffold itself is readiliy available by classical Biginelli three-component condensation, first reported in 1893 (see below). Both DHPM analogs, SQ 32926 (**4**) and SQ 32547 (**5**) are potent orally active antihypertensive agents.[5–7] In contrast to DHPs of the nifedipine type, however, such DHPM derivatives are inherently asymmetric.[5,6] A recent pharmacological study has suggested that here calcium channel modulation (calcium entry blocking *versus* activating) is dependent on the absolute configuration at the stereogenic center at C4, whereby the orientation of the C4-aryl group (*R* or *S* configuration) acts as a "molecular switch" between blocking and activating activity.[8] In SQ 32926 (**4**), for example, it is the (*R*)-enantiomer that carries the therapeutically desired calcium channel blocking (antagonist) activity.[5]



4, (*R*)-SQ 32926

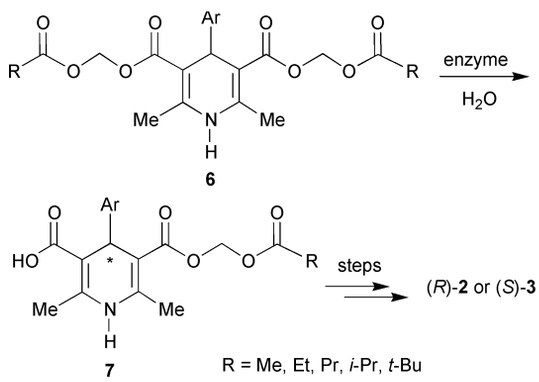


5, (*R*)-SQ 32547

Access to enantiomerically pure DHPs and DHPMs is therefore of considerable current interest. In the past, enantiomerically pure DHPMs were obtained by classical resolution of the corresponding carboxylic acids,[9] by separation of diastereo-

 DOI: 10.1039/b006372j

meric derivatives bearing chiral auxiliaries at N3,[5,6] or by enantioselective HPLC using chiral stationary phases.[10,11] In contrast, in the DHP series, enzymatic hydrolyses reactions have played a pivotal role in obtaining enantiomerically pure analogs.[12] In particular, the elegant desymmetrization approach developed by the Sih[13] and Achiwa[14] groups in the 1990's has found widespread use (Scheme 1). Here, a prochiral bis(acyloxymethyl) activated DHP bisester of type **6** was selectively hydrolyzed by different lipases in high chemical and optical yields.[12–14] Further manipulation of the obtained enantiomerically enriched monoester **7** provided a convenient entry into enantiomerically pure DHP calcium channel blockers such as (*R*)-nilvadipine (**2**),[15] or (*S*)-felodipine (**3**).[16] The use of acyloxymethyl derivatized carboxylic acids has been found to be a necessity since standard alkyl esters are not cleaved by lipases, presumably due to steric congestion and conjugation effects.[12–16]



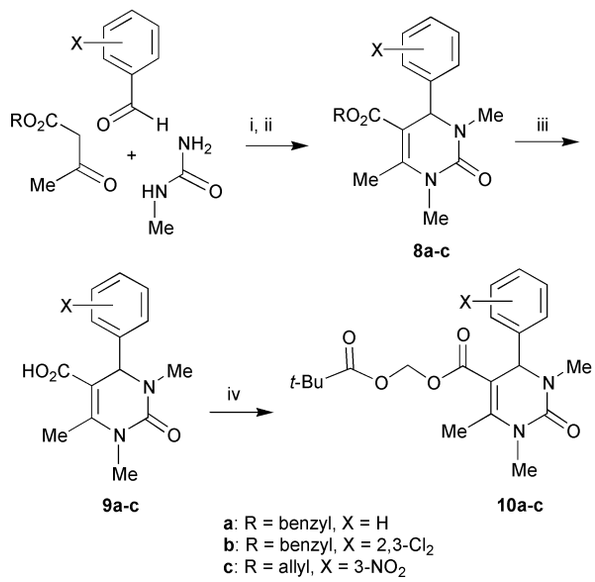
6 **7**

Scheme 1

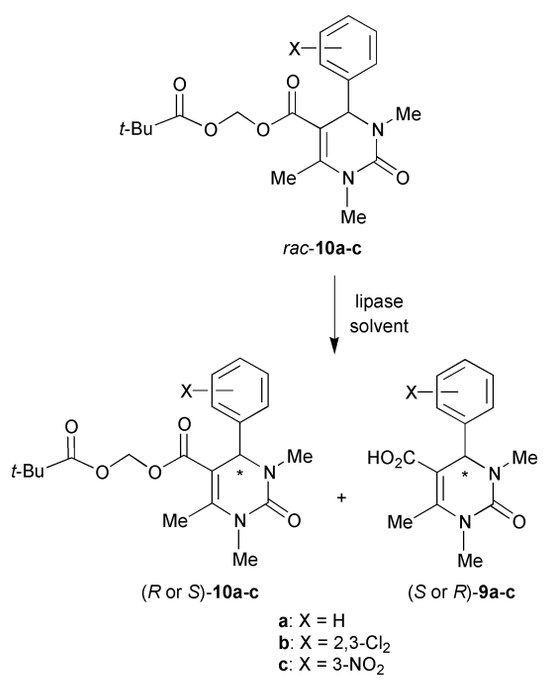
Due to the inherent asymmetry of DHPMs such as SQ 32926 (**4**) the above desymmetrization method is clearly inapplicable to this heterocyclic scaffold. In this article we present an alternative biocatalytic approach towards the preparation of enantiomerically pure DHPMs in full detail.[17]

Results and discussion

Although the above mentioned desymmetrization approach is not feasible in DHPMs, we considered it worthwhile to adopt the acyloxymethyl activation strategy shown in Scheme 1 towards a kinetic resolution method for DHPM C5-esters (see Scheme 3 below). In order to achieve the highest possible selectivities we initially chose to prepare the corresponding pivaloyloxymethyl (POM)-activated DHPM esters as model compounds. The synthesis of these esters proceeded in a straightforward manner and is outlined in Scheme 2: three-component Biginelli-type cyclocondensation[18] of an aromatic aldehyde with benzyl or allyl acetoacetate and *N*-methylurea using polyphosphate ester (PPE) in THF as reaction medium[19a] provided the corresponding *N*1-methyl-DHPMs in 85–93% yield and complete regioselectivity. In order to increase the lipophilicity of these DHPMs, an alkyl group was further introduced at the N3 amide functionality. Thus, *N*3-methylation with dimethyl sulfate[9] gave bis-(*N*-methyl)-DHPMs **8a**–**c** (*ca.* 85%) which were subsequently transformed into the corresponding DHPM acids **9a**–**c**. For benzyl esters **8a**,**b** this was achieved by hydrogenolysis over Pd/C;[9] in the case of allyl ester **8c** (X = NO_2) deallylation with Pd(0) under standard reaction conditions gave acid **9c** in 81% yield.[20] Catalytic removal of the benzyl group from the corresponding nitrophenyl DHPM benzyl ester was not possible without affecting reduction of the aromatic nitro group. The corresponding POM-activated esters **10a**–**c** were obtained from **9a**–**c** by treatment with commercially available pivaloyloxymethyl chloride (POM-Cl) in the presence of base in 74–96% yield.[21]



Scheme 2 *Reagents and conditions*: i, polyphosphate ester, THF, reflux, 24 h; ii, NaH, dimethyl sulfate, toluene, 70 °C, 6 h; iii for **a**,**b**, H_2, 10% Pd/C, 1 atm, Et_3N, MeOH, rt, 5 h; for **c**, Pd(PPh_3), morpholine, THF, rt, 20 h; iv, POM-Cl, Na_2CO_3, DMF, rt, 24 h.



Scheme 3

To our disappointment, and in contrast to the related DHP derivatives,[12–16] the lipase-catalyzed resolution of DHPM analogs (Scheme 3) exhibited lower selectivities in general with *E*-values not exceeding a value of ~50 (Table 1). Furthermore, the more lipophilic phenyl (**10a**) and dichlorophenyl derivatives (**10b**) gave better results than the nitrophenyl compound **10c**. Among various lipases, the enantiopreference showed an erratic behavior, *i.e.* depending on the system, either of the enantiomers was preferentially hydrolyzed. With substrate **10c**, best results were obtained with crude lipase Amano P ($E = 6.1$), while a partially purified enzyme preparation thereof (SAM-II) was completely non-selective. This low value could not be improved by medium engineering[22] through switching from aqueous diisopropyl ether to aqueous toluene. The sterically demanding dichloro derivative **10b** was hardly accepted by any of the lipases tested, except by lipase

Table 1 Lipase-screening on the hydrolysis of POM-DHPM esters **10a**–**c**[a]

DHPM	Lipase source	Solvent	Enantio-preference[b]	E[c]
10a	PLE (Amano A)	aq. Pr^i_2O	(*R*)	2.7
10a	PLE (Amano A)	aq. toluene	(*S*)	3.8
10a	*Candida rugosa* (Sigma)	aq. Pr^i_2O	(*S*)	4.2
10a	*Candida rugosa* (Sigma)	aq. toluene	(*S*)	49.0
10a	*Mucor miehei* (Biocatalysts)	aq. Pr^i_2O	(*S*)	1.4
10a	*Mucor miehei* (Biocatalysts)	aq. toluene	(*S*)	49.0
10b	*Penicillium roquefortii* (Amano R)	aq. Pr^i_2O	(*R*)[d]	19.0
10c	*Pseudomonas* sp. (Amano P)	aq. Pr^i_2O	(*R*)	6.1
10c	*Pseudomonas* sp. (SAM-II)	aq. Pr^i_2O	(*R*)	2.9

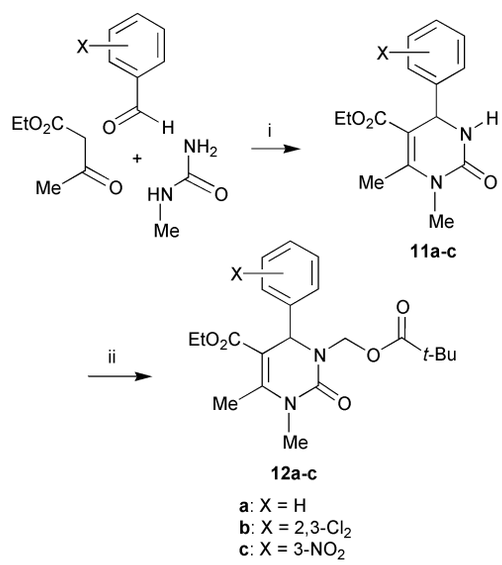
[a] For details, see Experimental section. [b] Excess enantiomer of **9**. [c] E = selectivity according to ref. 30. [d] (*R*)-enantiomer according to CIP nomenclature but homochiral to (*S*)-**9a**,**b**.

Amano R derived from *Penicillium roquefortii*, which exhibited a selectivity sufficient for preparative application ($E = 19$). Interestingly, this latter enzyme is only rarely used in preparative biotransformations. Compound **10a** is clearly the optimal substrate in this series, since it was converted by several enzymes in acceptable (lipase Amano AH, $E = 27$) or even good selectivities (lipases from *Candida rugosa* and *Mucor miehei*, $E = 49$). Interestingly, *Mucor* sp. lipase and porcine liver esterase showed an opposite enantiopreference to all other lipases. In addition, for **10a** medium engineering proved to be a powerful tool for selectivity enhancement. Thus, by switching from aqueous diisopropyl ether to aqueous toluene, selectivities increased considerably: for lipase AH ($E = 4 \rightarrow 27$), for lipase from *Candida rugosa* ($E = 4.2 \rightarrow 49$), and for *Mucor* sp. lipase ($E = 1.4 \rightarrow 49$).

The optical yields of substrates and products were determined by HPLC enantioseparation using a Chiralcel OD-H column (enantiomerically enriched acids **9a**–**c** were converted into the corresponding methyl esters by treatment with diazomethane prior to analysis).[10] In order to establish the enantiopreference in the biocatalytic experiments the absolute configuration of these methyl esters was determined by comparison of their CD spectra with reference samples of known absolute configuration as we have detailed elsewhere.[23] Despite the acceptable selectivities for some of the examples shown in Table 1, the corresponding conversion rates for these cases were too low (1–10%) to allow any meaningful preparative resolution experiments.

At this point we had to consider an alternative activation approach. The amide functionality present in dihydropyrimidones of the DHPM type in principle also allows the attachment of an acyloxymethyl residue at the *N*3 position (*i.e.* structure **12**) functioning as a "molecular handle". One apparent advantage of this set-up would be that the distance of the enzymatically cleavable ester functionality from the chiral center is reduced by two carbon atoms (*i.e.* from 6 to 4 bonds), which should lead to improved selectivities. Furthermore, enantioselective cleavage of the ester would lead to a hemiaminal which is expected to readily undergo chemical hydrolysis directly to the corresponding enantiopure *N*3-unsubstituted DHPM, thereby making further manipulations (*i.e.* of the C5 carboxy functionality) unnecessary. With this in mind we have prepared the corresponding *N*3-POM-activated DHPMs **12a**–**c** as shown in Scheme 4 following standard procedures.

Unfortunately, preliminary enzymatic screens using most of the lipases indicated in Table 1 soon made evident that DHPMs **12a**–**c** were rather resistant towards enzymatic hydrolysis, despite medium engineering and changes in reaction temperature. In order to increase conversion rates we have therefore synthesized some of the corresponding less bulky acetoxymethyl analogs, initially employing acetoxymethyl chloride instead of POM-Cl in the alkylation step. At the same time we also considered changing the N1-methyl substituent



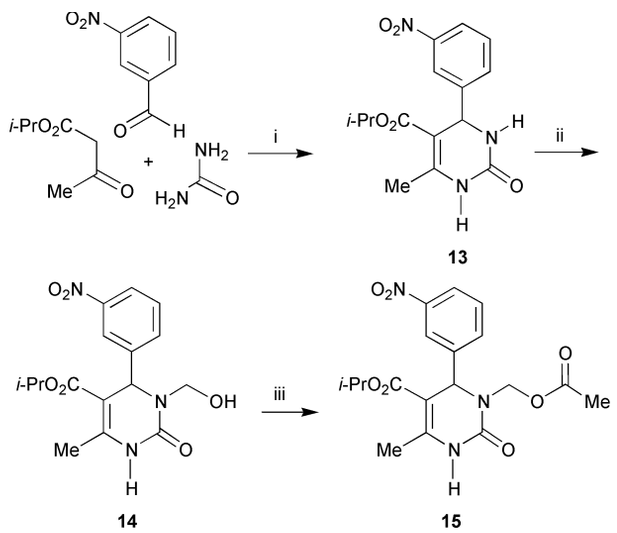
Scheme 4 *Reagents and conditions*: i, polyphosphate ester, THF, reflux, 24 h; ii, NaH, POM-Cl, toluene, 55 °C, 3 h.

(derived from *N*-methylurea) in activated DHPMs of type **12** for suitable protecting groups, which could be removed after the enzymatically cleavable ester functionality was introduced at N3. Since all known DHP and DHPM calcium channel modulators require the critical N1-position unblocked,[2–8] this issue needed to be addressed before any further refinement of the biocatalytic/synthetic strategy. After experimentation with a variety of protection groups that were introduced *via* the urea component in the Biginelli condensation (*N*-allyl or *N*-benzyl), we ultimately discovered an attractive alternative to avoid *N*1 protection altogether. As an alternative to the *N*-alkylation of amides with acyloxymethyl halides, several authors have reported that such activated esters could also be prepared in a two-step procedure by initial *N*-hydroxymethylation of the amide with formaldehyde under basic conditions, followed by standard acylation of the resulting *N*-hydroxymethyl derivative with acid chlorides.[24,25] In fact, this method generally provides higher yields than the direct alkylation procedure, in particular for *N*-acetoxymethylations. This two-step strategy has been initially developed and used successfully in biocatalytic kinetic resolutions of four-[24] and five-membered[25] lactams. In model studies with a variety of N1-unsubstituted DHPMs we have discovered that *N*-hydroxymethylation with 37% formaldehyde in ethanol in the presence of K_2CO_3 exclusively occurs at the N3 position, presumably due to the greater nucleophilicity of the N3 nitrogen as compared to the enamidic N1 nitrogen.[18] With this information in hand we have set out to develop a biocatalytic resolution method for the preparation of the orally active antihypertensive agent (*R*)-SQ 32926 (**4**).

Table 2 Lipase-screening on the hydrolysis of activated DHPM **15**[a]

Lipase source	Solvent	E[b]	C[c]	Ee[d]
Candida antarctica B (Novo Nordisk)	aq. Pr^i_2O	1.3	29	12
Geotrichum candidum (Amano GC)	aq. Pr^i_2O	1.7	21	23
Porcin pank. Lipase (Sigma)	aq. Pr^i_2O	7.6	36	68
Pseudomonas sp. (Amano P)	aq. Pr^i_2O	9.8	38	73
Rhizopus oryzae (Amano F)	aq. Pr^i_2O	10	38	75
Pseudomonas sp. (Amano AH)	aq. Pr^i_2O	13	36	79
Pseudomonas sp. (Amano AP6)	aq. Pr^i_2O	15	34	82
Mucor javanicus (Amano M)	aq. Pr^i_2O	25	40	87
Thermomyces lanuginosus (Amano CE)	aq. Pr^i_2O	43	46	90
Thermomyces lanuginosus (Amano CE)	aq. Pr^i_2O–Dextran	>200	51	96
Mucor javanicus (Amano M)	aq. Pr^i_2O–PEG	50	39	93
Mucor javanicus (Amano M)	aq. toluene/PEG	>200	15	99

[a] For details, see Experimental section. [b] E = selectivity. [c] C = conversion. [d] Ee = enantiomeric excess of product (*S*)-**14**.

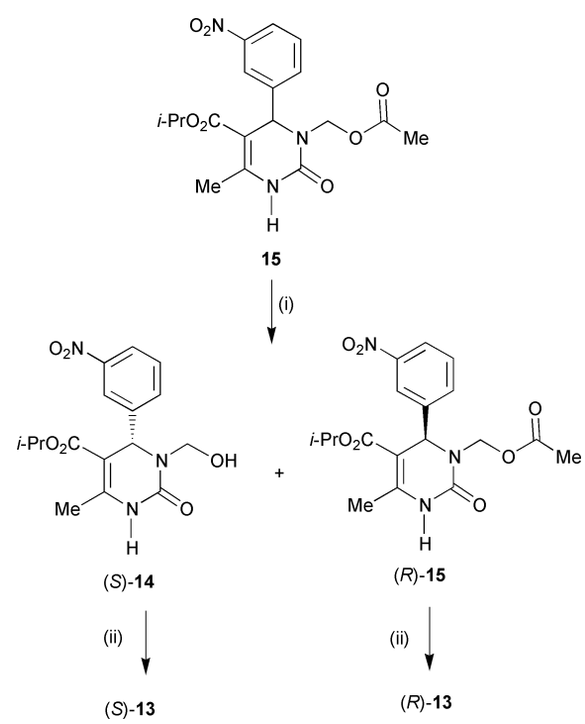


Scheme 5 *Reagents and conditions*: i, polyphosphate ester, THF, reflux, 24 h; ii, CH_2O (37% in H_2O), EtOH, K_2CO_3, reflux, 48 h; ii, AcCl, THF, Et_3N, 0 °C, 1 h.

The synthesis of the required acetoxymethyl activated DHPM **15** is presented in Scheme 5: Biginelli three-component cyclocondensation of isopropyl acetoacetate, 3-nitrobenzaldehyde, and urea again using polyphosphate ester (PPE) as reaction mediator[19] provided DHPM **13** in 94% yield, which has all the functionality of SQ 32926 (**4**) already set in place, except for the 3-carbamoyl group which can be introduced in one-step by treatment with trichloroacetyl isocyanate (see Scheme 7). As discussed above, N3-hydroxylmethylation of **13** was achieved by treating a solution of the DHPM in ethanol with aqueous formaldehyde (37%) and potassium carbonate at reflux temperature.[24a] This protocol consistently gave better results than other modifications reported in the literature, *i.e.* involving paraformaldehyde and/or sonication conditions.[25c] The resulting hemiaminal **14** is a crystalline compound which is surprisingly stable and could be purified by silica gel chromatography or *via* recrystallization from ethanol. It was also possible, however, to directly convert the crude hemiaminal **14** to the corresponding ester **15** by standard acylation with acetyl chloride in THF in the presence of triethylamine.[24a] The overall yield of the acetoxymethyl DHPM **15** over two steps from **13** was *ca*. 77%.

Having the required acetoxymethyl-activated DHPM **15** in hand we next tried a number of commonly used lipases and different solvent conditions for kinetic resolutions.

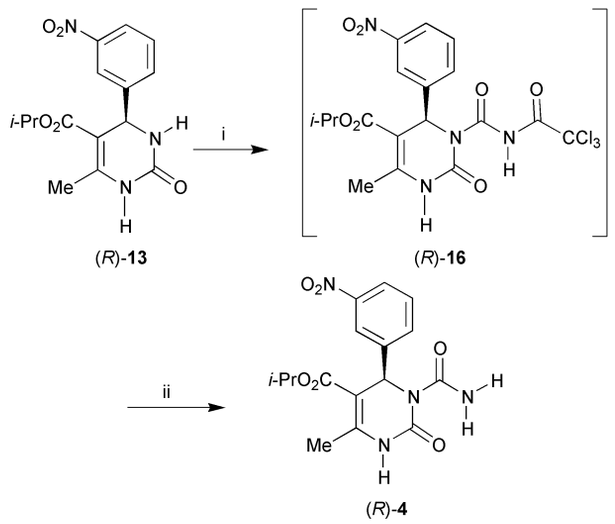
In contrast to substrates **10a**–**c**, compound **15** was well accepted by a range of lipases with reasonable reaction rates (Table 2). Quite surprisingly, many lipases showed low to moderate selectivities only, the exceptions being lipase from *Mucor javanicus* (Amano M, $E = 25$) and *Thermomyces lanuginosus* (Amano CE, $E = 43$). In order to improve these values even further, medium engineering was envisaged. Addition of an "enhancer" (such as dextran (MW 260000) or polyethylene glycol methyl ether (PEG) (MW 5000) led to the desired improvements ($E > 200$). After considerable further experimentation *Thermomyces lanuginosus* (Amano CE lipase) was identified as the biocatalyst of choice. The optimum solvent system was found to be diisopropyl ether–phosphate buffer (pH 7.0). Using dextran as additive[26] excellent enantioselectivities ($E > 200$) were achieved in a highly reproducible manner. After 3 days at 23 °C a 50 : 50 mixture of *N*3-hydroxymethyl DHPM (*S*)-**14** (96% ee) and *N*3-acetoxymethyl DHPM (*R*)-**15** (98% ee) was obtained after silica gel chromatography. This process was run several times on a gram scale giving identical results (see Experimental section). Importantly, both products from the kinetic resolution process could be deprotected in good yield and without any racemization by treatment with aqueous ammonia in methanol at 45 °C[25a] to furnish the *N*3-unsubstituted DHPMs (*S*)- and (*R*)-**13** respectively (Scheme 6).



Scheme 6 *Reagents and conditions*: i, *Thermomyces lanuginosus,* dextran, diisopropyl ether–buffer, rt, 72 h; ii, MeOH, NH_3, 45 °C, 48 h.

Having obtained (*R*)-**13** in acceptable enantiomeric purity (>98% ee) the conversion into the desired target compound (*R*)-**4** remained the last challenge in the synthesis. It should be

noted that the original preparation of *rac*- or (*R*)-SQ 32926 did not proceed through DHPM **13**, but through the corresponding *O*-methoxy derivative.[5,27] Treatment of this isourea derivative with phosgene or 4-nitrophenyl chloroformate, followed by ammonia provided the desired 3-carbamoyl DHPM.[27] In order to carbamoylate amide **13** a considerably more reactive carbamoylation agent was required. We have found that commercially available trichloroacetyl isocyanate is a very suitable reagent for this purpose.[28] Treatment of (*R*)-**13** with trichloroacetyl isocyanate in THF at room temperature for 24 h provided the unstable imide intermediate (*R*)-**16**, as identified by IR spectroscopy (ν_{max}/cm^{-1} 1790) (Scheme 7). Following addition

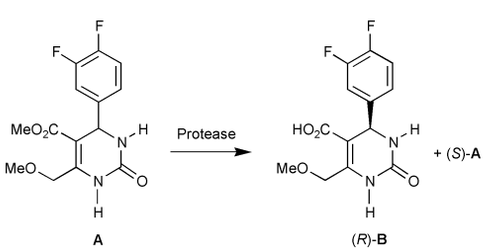


Scheme 7 *Reagents and conditions*: i, CCl_3CO–NCO, THF, rt, 24 h; ii, MeOH, SiO_2, rt, 48 h.

of methanol and silica gel to the reaction mixture[28b] hydrolysis of the imide to the desired amide took place smoothly (**16**→**4**), with an overall yield of 65%. The same sequence of reactions was also carried out with the corresponding (*S*)-enantiomer and with the racemate (see Experimental section). Note that this synthetic protocol to *rac*-**4** constitutes a novel two-step preparation (→**13**→**4**) of SQ 32926, which is a clear improvement over the existing multistep procedure.[27] The absolute configuration and enantiomeric purity of (*R*)-**4** and of related compounds was established by CD spectroscopy and chiral HPLC measurements, respectively.[17]

In conclusion, we have developed a novel chemoenzymatic synthesis for enantiomerically pure dihydropyrimidine derivatives that is based on a lipase-catalyzed kinetic resolution. While the attempted adoption of an activation strategy developed originally for dihydropyridines of the Hantzsch-type gives unsatisfactory results (Scheme 3), the modified activation protocol introduced herein, involving the introduction of an enzymatically cleavable ester functionality at the urea moiety of the dihydropyrimidone scaffold, allows the resolution of such dihydropyrimidones with high selectivities.†

† While this work was in progress the direct protease-catalyzed resolution (*e.g.* using subtilisin) of DHPM **A** was also reported. See ref. 29.



Experimental

General procedures and materials

Mps were determined on a Gallenkamp melting point apparatus, Mod. MFB-595 and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-200 Gemini or a Bruker AMX 360 instrument (*J* values are given in Hz). Micro-analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F-252 (Merck) plates. Flash chromatography was performed with silica gel 60 (40–63 μm, Aldrich) using mixtures of light petroleum and ethyl acetate as eluent. Optical rotations were measured on a Perkin-Elmer Polarimeter using a 10 cm Microcell. Circular dichroism (CD) measurements were carried out on a JASCO J-715 CD spectropolarimeter at 20 °C using a 1 mm quartz cell with a volume of 350 μl. The following instrument settings were used: band width 1.0 nm, resolution 1 nm, accumulation 2, sensitivity 20 mdeg, response 1 s, speed 100 nm min^{-1}. Dihydropyrimidines **8a**,[9] **9a**,[9] **11a**,[19a] and **13**[19b] were prepared according to literature procedures. PEG (MW 5000, Aldrich 20,151-7), and dextran (MW 260000, Sigma D-7265) were used as provided by the supplier.

HPLC analysis

High performance liquid chromatographic measurements employed a Hewlett Packard HP 1050 compact system with variable wavelength detector (VWL) and a HP ^{2D}HPLC Chemstation version A.02.05. The chiral stationary phases used for the direct analysis were either a Chiralcel OD-H column (J. T. Baker, Netherlands) (250 × 4.6 mm id), a Chiralpak AD column (Daicel, Japan) (250 × 4.6 mm id), or a 3*S*,4*R*-Whelk-O1 column (Merck, Darmstadt) (250 × 4.6 mm id). The temperature during the separation was adjusted to 20 °C and UV detection performed at 254 nm. Solvent systems, flow rates, and retention times are noted at the respective entries below.

Benzyl 4-(2,3-dichlorophenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 8b

A mixture containing benzyl acetoacetate (1.92 g, 10 mmol), 2,3-dichlorobenzaldehyde (1.75 g, 10 mmol), *N*-methylurea (1.11 g, 15 mmol) and freshly prepared polyphosphate ester (PPE)[19] (1.58 g) in abs. THF (20 cm^3) was heated under reflux for 24 h. The reaction mixture was poured onto ice, the precipitated solid was filtered and washed twice with cold ethanol to yield benzyl 4-(2,3-dichlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3.81 g, 93%) as a colorless solid, mp 128–131 °C (Found: C, 59.38; H, 4.41; N, 6.87; $C_{20}H_{18}Cl_2N_2O_3$ requires: C, 59.27; H, 4.48; N, 6.91%); ν_{max}/cm^{-1} 1700, 1680, 1625; δ_H (200 MHz; $CDCl_3$) 2.57 (3 H, s, CH_3), 3.14 (3 H, s, NCH_3), 4.90–5.10 (2 H, m, OCH_2Ph), 5.70 (1 H, d, *J* 3.5, C4-H), 6.90–7.60 (8 H, m, ArH), 8.0 (1H, d, *J* 3.5, NH).

A suspension of the above DHPM (3.60 g, 8.90 mmol) with NaH (0.40 g of a 60% dispersion in mineral oil, 10 mmol) in dry toluene (100 cm^3) was heated at 70 °C for 30 min until a yellow solid precipitated. Dimethyl sulfate (1.90 g, 15 mmol) was added and the mixture was stirred until the solid dissolved again. After completion of the reaction (3–6 h, TLC monitoring), the mixture was cooled to ambient temperature, ice–water (100 cm^3) was added and the mixture was neutralized with 1 M HCl. The organic phase was separated, washed with water (3×) and evaporated. The resulting crude product was recrystallized from ethanol to yield **8b** (3.52 g, 84%) as a colorless solid, mp 114 °C (Found: C, 60.24; H, 4.68; N, 6.60; $C_{21}H_{20}Cl_2N_2O_3$ requires C, 60.15; H, 4.81; N, 6.68%);

ν_{max}/cm^{-1} 1700, 1670, 1630; δ_H (200 MHz; $CDCl_3$) 2.60 (3 H, s, CH_3), 2.90 (3 H, s, NCH_3), 3.30 (3 H, s, NCH_3), 4.90–5.15 (2 H, m, OCH_2Ph), 5.90 (1 H, s, C4-H), 7.00–7.40 (8 H, m, ArH).

Allyl 4-(3-nitrophenyl)-1,3,6-trimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 8c

This compound was prepared by PPE-mediated Biginelli condensation in a similar manner to that described above for DHPM **8b** using allyl acetoacetate, 3-nitrobenzaldehyde and *N*-methylurea as starting materials. Allyl 1,6-dimethyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was obtained as a colorless solid (85%), mp 125–126 °C (Found: C, 58.30; H, 5.11; N, 12.50; $C_{16}H_{17}N_3O_5$ requires C, 58.00; H, 5.17; N, 12.68; ν_{max}/cm^{-1} 1710–1670, 1630; δ_H (200 MHz; $CDCl_3$) 2.51 (3 H, s, CH_3), 3.20 (3 H, s, NCH_3), 4.52 (2 H, m, CH_2-CH=CH$_2$), 5.10–5.20 (2 H, m, CH_2-CH=CH$_2$), 5.45 (1 H, d, *J* 3.5, C4-H), 5.70–5.90 (1 H, m, CH$_2$-CH=CH$_2$), 6.82 (1 H, d, *J* 3.5, NH), 7.30–7.60 (2 H, m, ArH), 8.00–8.10 (2 H, m, ArH).

A solution of the above DHPM (2.88 g, 8.70 mmol) in abs. toluene (10 cm^3) was added dropwise to a suspension of NaH (0.60 g of a 60% dispersion in mineral oil, 15 mmol) and dimethyl sulfate (1.10 g, 8.7 mmol) in abs. toluene (30 cm^3) and was stirred at room temperature for 2 h. After completion of the alkylation (TLC monitoring) water was added to the reaction mixture, the organic layer was twice extracted with water, dried (Na_2SO_4) and evaporated. The crude product was recrystallized from ethanol to yield DHPM **8c** (2.55 g, 85%) as a pale yellow solid, mp 126–127 °C (Found: C, 59.28; H, 5.75; N, 12.22; $C_{16}H_{17}N_3O_5$ requires; C, 59.12; H, 5.55; N, 12.17); ν_{max}/cm^{-1} 1670,1530; δ_H (200 MHz; $CDCl_3$) 2.50 (3 H, s, CH_3), 2.95 (3 H, s, NCH_3), 3.30 (3 H, s, NCH_3), 4.60 (2 H, m, CH_2-CH=CH$_2$), 5.20–5.30 (2 H, m, CH$_2$-CH=CH_2), 5.35 (1 H, s, C4-H), 5.80–6.00 (1 H, m, CH$_2$–CH=CH$_2$), 7.40–7.60 (2 H, m, ArH), 8.05–8.15 (2H, m, ArH).

4-(2,3-Dichlorophenyl)-2-oxo-1,3,6-trimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid 9b

To a solution of DHPM **8b** (4.19 g, 10 mmol) in methanol (50 cm^3) and triethylamine (1.00 g; 10 mmol) was added a catalytic amount of 10% Pd/C and the reaction mixture was hydrogenated for 5 h at room temperature. After completion of the reaction (TLC-monitoring) the solution was filtered from the catalyst, evaporated, and the residue was treated with 2 M HCl to yield the free carboxylic acid. After washing with water, the acid was recrystallized from ethanol to yield **9b** (2.89 g, 88% yield), mp 232 °C (dec.) (Found: C, 51.18; H, 4.09; N, 8.42; Cl, 21.36; $C_{14}H_{14}Cl_2N_2O_3$ requires: C, 51.08; H, 4.29; N, 8.60; Cl, 21.54); ν_{max}/cm^{-1} 1700, 1630; δ_H (200 MHz; $CDCl_3$) 2.49 (3 H, s, CH_3), 2.80 (3 H, s, NCH_3), 3.21 (3 H, s, NCH_3), 5.82 (1 H, s, C4-H), 7.30–7.60 (3 H, m, ArH).

4-(3-Nitrophenyl)-2-oxo-1,3,6-trimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid 9c

To a solution of DHPM **8c** (3.06 g, 8.6 mmol) and Pd(PPh$_3$)$_4$ (250 mg, 0.22 mmol) in THF abs. (40 cm^3), morpholine (12.7 g, 146 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 20 h and afterwards poured into CH_2Cl_2. The solution was extracted twice with 2 M HCl. The organic layer was then extracted twice with saturated $NaHCO_3$ and these combined, basic, yellow aqueous layers acidified with 1 M HCl and re-extracted 3× with CH_2Cl_2. These organic layers were dried over Na_2SO_4 and evaporated. The crude product was recrystallized from ethanol to yield the pale yellow acid **9c** (2.20 g, 81%), mp 163 °C (dec.) (Found: C, 55.14; H, 4.93; N, 13.56; $C_{14}H_{15}N_3O_5$ requires: C, 55.10; H, 5.00; N, 13.80; ν_{max}/cm^{-1} 1670, 1630, 1600; δ_H (200 MHz; $CDCl_3$) 2.51 (3 H, s, CH_3), 2.85 (3 H, s, NCH_3), 3.20 (3 H, s, NCH_3), 5.45 (1 H, s, C4-H), 7.70 (2 H, m, ArH), 8.10–8.20 (2 H, m, ArH).

Pivaloyloxymethyl 2-oxo-4-phenyl-1,3,6-trimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 10a

A suspension of DHPM **9a** (1.80 g, 7.0 mmol), pivaloyloxymethyl chloride (2.20 g, 15 mmol) and Na_2CO_3 (0.74 g, 7.0 mmol) in abs. DMF (50 cm^3) was stirred at room temperature for 1 d. After completion (TLC monitoring), the suspension was poured into a mixture of ethyl acetate and water. The organic layer was extracted twice with water, dried (Na_2SO_4) and evaporated. The crude solid was recrystallized from ethanol to yield DHPM **10a** (2.60 g, 95%) as a colorless solid, mp 106–108 °C (Found: C, 64.08; H, 7.22; N, 7.45; $C_{20}H_{26}N_2O_5$ requires: C, 64.10; H, 7.00; N, 7.50%); ν_{max}/cm^{-1} 1745, 1720, 1670, 1620; δ_H (200 MHz; $CDCl_3$) 1.15 (9 H, s, 3 CH_3-C), 2.52 (3 H, s, CH_3), 2.91 (3 H, s, NCH_3), 3.29 (3 H, s, NCH_3), 5.25 (1 H, s, C4-H), 5.71–5.85 (2 H, m, CH_2-O), 7.15–7.30 (5 H, m, ArH); δ_C (90 MHz; DMSO) 16.3, 26.4, 30.7, 34.0, 38.1, 59.8, 78.9, 101.0, 126.5, 127.8, 128.6, 140.7, 152.4, 152.7, 163.8, 176.2.

Pivaloyloxymethyl 4-(2,3-dichlorophenyl)-2-oxo-1,3,6-trimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 10b

This compound was prepared in a similar manner to analog **10a** described above, using DHPM **9b** as a starting material. The pivaloyloxymethyl ester **10b** (96% yield) was obtained as a colorless solid, mp 155–156 °C (Found: C, 54.45; H, 5.44; N, 6.24; Cl, 16.01; $C_{20}H_{24}Cl_2N_2O_5$ requires: C, 54.21; H, 5.30; N, 6.33; Cl, 16.03%); ν_{max}/cm^{-1} 1720, 1670, 1620; δ_H (200 MHz; $CDCl_3$) 1.04 (9 H, s, 3 CH_3-C), 2.58 (3 H, s, CH_3), 2.93 (3 H, s, NCH_3), 3.31 (3 H, s, NCH_3), 5.65–5.75 (2 H, m, CH_2-O), 5.91 (1 H, s, C4-H), 7.10–7.40 (3 H, m, ArH).

Pivaloyloxymethyl 4-(3-nitrophenyl)-2-oxo-1,3,6-trimethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 10c

This compound was prepared in a similar manner to analog **10a** described above, using DHPM **9c** as starting material. The pivaloyloxymethyl ester **10c** (74% yield) was obtained as a colorless solid, mp 109–110 °C (Found: C, 57.42, H, 6.11, N 9.97; $C_{20}H_{25}N_3O_7$ requires: C, 57.27; H, 6.01; N, 10.02%); ν_{max}/cm^{-1} 1750, 1720, 1670, 1620; δ_H (200 MHz; $CDCl_3$) 1.11 (9 H, s, 3 CH_3-C), 2.55 (3 H, s, CH_3), 2.91 (3 H, s, NCH_3), 3.32 (3 H, s, NCH_3), 5.30 (1 H, s, C4-H), 5.70–5.80 (2 H, m, CH_2-O), 7.40–7.60 (2 H, m, ArH), 8.05–8.15 (2 H, m, ArH).

Enzyme screening with DHPMs 10a–c and 15

Toluene–aqueous buffer as solvent: lipases (50 mg, see Table 1) were rehydrated for 1 h in aqueous buffer (0.5 ml, 50 mmol $NaHPO_4$, pH 7.00). Then a solution of the corresponding DHPM *rac*-**10a**–**c** (*ca*. 25 mg) in toluene (0.5 ml) was added and the reaction mixture was shaken (200 rpm) for 3 days.

Diisopropyl ether as solvent: DHPMs *rac*-**10a**–**c** (*ca*. 10 mg) was dissolved in diisopropyl ether (1 ml) (saturated with aqueous buffer, 50 mmol $NaHPO_4$, pH 7.00), and after addition of lipases (*ca*. 50 mg, see Table 1) were shaken for 3 days.

After monitoring the conversion of the substrates by TLC (toluene–acetone 3 : 1), each suspension was centrifuged and the organic layer separated. After evaporation of the solvent, the precipitate was dissolved in CH_2Cl_2 (0.5 ml) and extracted with saturated $NaHCO_3$ solution (0.5 ml). The organic layer containing the activated ester was evaporated again and the precipitate was analyzed by direct enantioselective HPLC using a Chiralcel OD-H column. The aqueous layer was washed three times with CH_2Cl_2, and subsequently was acidified by addition of 2 M HCl to pH 3. The corresponding DHPM acid was reextracted with CH_2Cl_2, converted to its methyl ester by

treatment with diazomethane, and subsequently analyzed by HPLC using a Chiralcel OD-H column which allowed the calculation of selectivities (see Table 1).

Similar screening experiments were performed with *rac*-**15** although here no extraction and subsequent methylation with diazomethane was necessary. The selectivities were determined by direct HPLC analysis (Chiralpak AD column).

Ethyl 4-(2,3-dichlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 11b

This compound was prepared by PPE-mediated Biginelli condensation[19a] in an analogous manner to that described for DHPM **8b** above, using ethyl acetoacetate (1.30 g, 10 mmol) 2,3-dichlorobenzaldehyde (1.75 g, 10 mmol) and *N*-methylurea (1.11 g, 15 mmol) as starting materials. DHPM **11b** (3.17 g, 93%) was obtained as a colorless solid, mp 186–188 °C (Found: C, 52.61; H, 4.62; N, 8.29; $C_{15}H_{16}Cl_2N_2O_3$ requires: C, 52.49, H, 4.67; N, 8.16%); ν_{max}/cm^{-1} 1690, 1625; δ_H (360 MHz; $CDCl_3$) 1.07 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 2.65 (3 H, s, CH$_3$), 3.22 (3 H, s, NCH$_3$), 4.03 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 5.83 (2 H, m, C4-H and N3-H), 7.06–7.41 (3 H, m, ArH).

Ethyl 1,6-dimethyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidne-5-carboxylate 11c

This compound was prepared by PPE-mediated Biginelli condensation[1a] in an analogous manner to that described for DHPM **8b** above, using ethyl acetoacetate (1.30 g, 10 mmol), 3-nitrobenzaldehyde (1.51 g, 10 mmol) and *N*-methylurea (1.11 g, 15 mmol) as starting materials. DHPM **11c** (2.84 g, 88%) was obtained as a colorless solid, mp 143–145 °C (Found: C, 56.21; H, 5.01; N, 13.16; $C_{15}H_{17}N_3O_5$ requires: C, 56.43; H, 5.33; N, 13.17%); ν_{max}/cm^{-1} 1680, 1620; δ_H (360 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 2.57 (3 H, s, CH$_3$), 3.25 (3 H, s, NCH$_3$), 4.13 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 5.50 (1 H, s, C4-H), 6.59 (1 H, s, NH), 7.45–7.59 (2 H, m, ArH), 8.09–8.13 (2 H, m, ArH).

Ethyl 1,6-dimethyl-2-oxo-4-phenyl-3-pivaloyloxymethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 12a

To a suspension of NaH (0.20 g of 60% dispersion in mineral oil, 5.0 mmol) in dry toluene (20 cm^3), pivaloyloxymethyl chloride (0.54 g, 3.6 mmol) and DHPM **11a** (0.82 g, 3.0 mmol) was added. After stirring for 3 h at 55–60 °C bath temperature the suspension was allowed to cool to room temperature and saturated aqueous NH_4Cl (20 cm^3) was added. The mixture was stirred for another 10 minutes, the organic phase was separated, washed twice with water, dried (Na_2SO_4) and evaporated under reduced pressure. The oily residue was crystallized by treatment with methanol–water 3 : 1 to yield **12a** (0.88 g, 76%) as a colorless solid, mp 78–79 °C (Found: C, 65.28; H, 7.60; N, 7.11; $C_{21}H_{28}N_2O_5$ requires: C, 64.95; H, 7.21; N, 7.21%); ν_{max}/cm^{-1} 1740, 1680, 1625; δ_H (360 MHz; $CDCl_3$) 1.03 (9 H, s, 3 CH$_3$-C), 1.25 (3 H, t, J 7.5, C*H*$_3$-CH$_2$), 2.47 (3 H, s, CH$_3$), 3.21 (3 H, s, NCH$_3$), 4.16 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 5.38–5.60 (3 H, m, NCH$_2$, C4-H), 7.25 (5 H, m, ArH); δ_C (90 MHz; DMSO) 13.9, 15.9, 26.4, 30.8, 38.1, 58.3, 59.8, 71.9, 104.7, 126.4, 127.7, 128.5, 141.9, 149.1, 152.8, 164.9, 177.1.

Ethyl 4-(2,3-dichlorophenyl)-1,6-dimethyl-2-oxo-3-pivaloyloxymethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 12b

This compound was prepared in a similar manner to analog **12a** described above employing DHPM **11b** as starting material to give **12b** (89%) as a colorless solid, mp 87–88 °C (Found: C, 55.17; H, 5.90; N, 6.04; $C_{21}H_{26}Cl_2N_2O_5$ requires: C, 55.15; H, 5.69; N, 6.13%); ν_{max}/cm^{-1} 1735, 1710, 1675, 1630; δ_H (360 MHz; $CDCl_3$) 1.00 (9 H, s, 3 CH$_3$-C), 1.49 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 2.58 (3 H, s, CH$_3$), 3.33 (3 H, s, NCH$_3$), 4.06 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 5.40–5.60 (2 H, m, NCH$_2$), 6.10 (1 H, s, C4-H), 7.12–7.40 (3 H, m, ArH).

Ethyl 1,6-dimethyl-4-(3-nitrophenyl)-2-oxo-3-pivaloyloxymethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 12c

This compound was prepared in a similar manner to analog **12a** described above using DHPM **11c** as starting material to yield **12c** (66%) as a colorless solid, mp 88–89 °C (Found: C, 58.24; H, 6.40; N, 9.63; $C_{21}H_{27}N_3O_7$ requires: C, 58.19; H, 6.23; N, 9.70%); ν_{max}/cm^{-1} 1730, 1710, 1680, 1620; δ_H (360 MHz; $CDCl_3$) 1.00 (9 H, s, 3 CH$_3$-C), 1.30 (3 H, t, *J* 7.5, C*H*$_3$-CH$_2$), 2.51 (3 H, s, CH$_3$), 3.30 (3 H, s, NCH$_3$), 4.19 (2 H, q, *J* 7.5, C*H*$_2$-CH$_3$), 5.49–5.50 (2 H, m, NCH$_2$), 5.65 (1 H, s, C4-H), 7.48 (2 H, m, ArH), 8.16 (2 H, m, ArH).

Isopropyl 3-hydroxymethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 14

A mixture of DHPM **13** (3.84 g, 12.0 mmol), aqueous formaldehyde (9.0 g, 37%, 110 mmol), K_2CO_3 (0.96 g, 7.0 mmol) and ethanol (30 cm^3) was heated under reflux for 48 hours. The solvent was evaporated under reduced pressure and the crude product triturated with ether to give **14** (3.81 g, 91%) as a colorless solid. An analytical sample was prepared by recrystallization from ethanol, mp 159–162 °C (Found: C, 55.03; H, 5.50; N, 12.02; $C_{16}H_{19}N_3O_6$ requires: C, 55.01; H, 5.44; N, 12.03%); ν_{max}/cm^{-1} 1710, 1675, 1640; δ_H (200 MHz; DMSO) 1.04 (3 H, d, *J* 6.0, C*H*$_3$-CH), 1.22 (3 H, d, *J* 6.0, C*H*$_3$-CH), 2.25 (3 H, s, CH$_3$), 4.10–4.25 (1 H, dd, *J* 2.5 and 8.5, NCH$_2$), 4.78–4.91 (1 H, m, C*H*-CH$_3$), 5.04-5.17 (1 H, dd, *J* 2.5 and 8.5, NCH$_2$), 5.61 (1 H, s, C4-H), 6.05 (1 H, t, *J* 7.5, OH) 7.60–7.78 (2 H, m, ArH), 8.10–8.20 (2 H, m, ArH), 9.58 (1 H, s, NH).

Isopropyl 3-acetoxymethyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate 15

To a stirred solution of DHPM **14** (2.09 g, 6.0 mmol) and Et_3N (1.25 g, 12.0 mmol) in abs. THF (50 cm^3), acetyl chloride (1.18 g, 15 mmol) was slowly added at 0–5 °C. After stirring for 1 hour at this temperature the solvent was evaporated under reduced pressure, the residue triturated with dichloromethane (40 cm^3) and extracted once with water (30 cm^3) and twice with brine (30 cm^3). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was trituated with a small amount of ethanol. The crude product was purified by flash chromatography (light petroleum–EtOAc, 1 : 1) to yield DHPM **15** (1.70 g, 72%) as a colorless solid, mp 147–149 °C (Found: C, 55.17; H, 5.55; N, 10.69; $C_{18}H_{21}N_3O_7$ requires: C, 55.24; H, 5.37; N, 10.74%); ν_{max}/cm^{-1} 1750, 1705 1690, 1640; δ_H (200 MHz; $CDCl_3$) 1.10 (3 H, d, *J* 6.0, C*H*$_3$-CH), 1.26 (3 H, d, *J* 6.0, C*H*$_3$-CH), 1.90 (3 H, s, CH$_3$CO), 2.38 (3 H, s, CH$_3$), 4.90–5.06 (1H, m, C*H*-CH$_3$), 5.23 (1 H, m, NCH$_2$), 5.55–5.69 (2 H, m, NCH$_2$ and C4-H), 7.45–7.55 (1 H, m, ArH), 7.70–7.78 (1 H, m, ArH), 8.10–8.25 (2 H, m, ArH), 8.50 (1 H, s, NH); δ_C (90 MHz; DMSO) 18.4, 21.1, 22.2, 22.5, 60.0, 67.9, 71.1, 101.5, 122.5, 123.5, 131.1, 134.2, 145.8, 148.4, 148.6, 152.2, 164.8, 170.8.

Enantioselective enzymatic hydrolysis of DHPM 15

Thermomyces lanuginosus (Amano CE lipase, 400 mg) was rehydratized in phosphate buffer (35 cm^3, 50 mmol, pH = 7) containing 5% of dextran (*Leuconostoc mesenteroides*, MW 260000). Then DHPM **15** (200 mg) in diisopropyl ether (200 cm^3) was added. The mixture was shaken at 180 rpm at 23 °C for 72 hours. After controlling the conversion by HPLC (51%) (Chiralpak AD, heptane–propan-2-ol 89 : 11, flow = 0.5 ml min^{-1}) the organic layer was separated, washed with water, dried, evaporated to dryness and purified by flash chromatography (light petroleum–EtOAc 1 : 2) to yield (*R*)-**15** (R_f = 0.43, 90 mg, 90%, mp 127–129 °C, 98% ee, (Chiralpak AD, heptane–propan-2-ol 89 : 11, flow = 0.5 ml min^{-1},

(R) = 31.76 min, (S) = 37.00 min), $[\alpha]_D = -165.2$ (c 1.0, MeOH)) and (S)-**14** ($R_f = 0.17$, 88 mg, 99%, mp 186–188 °C, 96% ee (Chiralpak AD, heptane–propan-2-ol 89 : 11, flow = 0.5 ml min^{-1}, (R) = 28.89 min, (S) = 42.21 min), $[\alpha]_D = +206.5$ (c 1.0, MeOH)). The IR and ^{1}H-NMR spectra of these samples were identical to those of the corresponding racemates (see above).

Isopropyl (4*R*)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (*R*)-13

A suspension of DHPM (*R*)-**15** (0.54 g, 1.4 mmol) in methanol (15 cm^3) and conc. ammonia (10 cm^3) was stirred for 48 hours at 45 °C. The solvent was evaporated and the residue triturated with water and stirred at room temperature for 2 hours. The product was filtered by suction to yield (*R*)-**13** (0.32 g, 73%) as a colorless solid, mp 201–203 °C, 98% ee (Chiralpak AD, heptane–propan-2-ol 70 : 30, flow = 0.8 ml min^{-1}, (R) = 8.01 min, (S) = 10.64 min), $[\alpha]_D = -89.3$ (c 1.0, MeOH). IR and ^{1}H-NMR data were identical to those of the racemate.[19b]

Isopropyl (4*S*)-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (*S*)-13

This compound was prepared in a similar manner to enantiomer (*R*)-**13** described above, using (*S*)-**14** (0.53 g, 1.5 mmol) as starting material. An analytical sample of DHPM (*S*)-**13** (0.40 g, 83%) was prepared by flash chromatography (light petroleum–EtOAc 2 : 1), mp 201–203 °C, 96% ee (Chiralpak AD, heptane–propan-2-ol 70 : 30, flow = 0.8 ml min^{-1}, (R) = 8.01 min, (S) = 10.64 min), $[\alpha]_D = +79.1$ (c 0.5, MeOH). IR and ^{1}H-NMR data were identical to those of the racemate.[19b]

Isopropyl (4*R*)-3-aminocarbonyl-6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (*R*)-4

To a solution of DHPM (*R*)-**13** (0.32 g, 1.0 mmol) in tetrahydrofuran (10 cm^3) trichloroacetyl isocyanate (0.24 ml, 2.0 mmol) was added dropwise. After stirring for 24 hours all starting material was consumed (TLC-monitoring) and imide (*R*)-**16** was formed according to an IR spectrum taken from a small isolated solid sample (ν_{max}/cm^{-1} 1790). In order to hydrolyze the imide methanol (10 cm^3) and silica gel (1 g) were added. The suspension was stirred for 48 h at rt, then diluted with acetone, filtered and evaporated to dryness. The crude product was purified by flash chromatography (light petroleum–EtOAc 1 : 1) to provide (*R*)-**4** (0.24 g; 65%) as a colorless solid mp 161–164 °C (lit.[5] mp 160–161 °C), 98% ee (Whelk 01, heptane–propan-2-ol 70 : 30, flow = 0.5 ml min^{-1}, (R) = 16.20 min, (S) = 19.12 min) (Found: C, 52.73; H, 4.71; N, 15.22; $C_{16}H_{18}N_4O_6$ requires: C, 53.04; H, 4.97; N, 15.47%); ν_{max}/cm^{-1} 1725, 1710 1650; δ_H (200 MHz; DMSO) 1.14 (3 H, d, J 6.0, CH_3-CH), 1.24 (3 H, d, J 6.0, CH_3-CH), 2.30 (3 H, s, CH_3), 4.90–5.06 (1H, m, CH-CH_3), 6.58 (1 H, s, C4-H), 7.58–7.70 (3 H, m, ArH), 8.08 (1 H, s, ArH), 8.10–8.22 (2 H, m, NH_2) 10.20 (1 H, s, NH); $[\alpha]_D = -136.7$ (c = 1, MeOH) (lit.[5] $[\alpha]_D = -147.4$ (c = 1, MeOH).

DHPMs (*S*)-**4** (mp 161–164 °C) (lit.[5] 160–161 °C), and *rac*-**4** (mp 209–210 °C) (lit.[27] 206–207 °C)) were prepared in an analogous fashion.

Acknowledgements

This work was supported by the "Jubiläumsfonds der Österreichischen Nationalbank" (Project 7904), and the Austrian Science Fund (FWF, Projects P-11994-CHE and F115). The authors wish to express their cordial thanks to Amano Pharm. Co. for their generous donation of enzymes.

References

1 Part 22, A. Stadler and C. O. Kappe, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1363.
2 R. A. Janis, P. J. Silver and D. J. Triggle, *Adv. Drug Res.*, 1987, **16**, 309.
3 F. Bossert and M. Vater, *Med. Res. Rev.*, 1989, **9**, 291.
4 S. Goldman and J. Stoltefuss, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1559.
5 K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.
6 G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz and M. F. Malley, *J. Med. Chem.*, 1992, **35**, 3254.
7 G. J. Grover, S. Dzwonczyk, D. M. McMullen, C. S. Normadinam, P. G. Sleph and S. Moreland, *J. Cardiovasc. Pharmacol.*, 1995, **26**, 289.
8 G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem.*, 1995, **38**, 119.
9 C. O. Kappe, G. Uray, P. Roschger, W. Lindner, C. Kratky and W. Keller, *Tetrahedron*, 1992, **48**, 5473.
10 O. P. Kleidernigg and C. O. Kappe, *Tetrahedron: Asymmetry*, 1997, **8**, 2057.
11 K. Lewandowski, P. Murer, F. Svec and J. M. J. Fréchet, *J. Comb. Chem.*, 1999, **1**, 105.
12 For a recent review, see: S. Marchalín, M. Chudík, V. Mastihuba and B. Decroix, *Heterocycles*, 1998, **48**, 1943.
13 X. K. Holdgrün and C. J. Sih, *Tetrahedron Lett.*, 1991, **32**, 3465.
14 H. Ebiike, Y. Terao and K. Achiwa, *Tetrahedron Lett.*, 1991, **32**, 5805.
15 H. Ebiike and K. Achiwa, *Tetrahedron: Asymmetry*, 1994, **5**, 1447.
16 Y. Yamazaki, H. Ebiike and K. Achiwa, *Chem. Pharm. Bull.*, 1994, **42**, 1968.
17 For a preliminary communication, see: B. Schnell, U. T. Strauss, P. Verdino, K. Faber and C. O. Kappe, *Tetrahedron: Asymmetry*, 2000, **11**, 1449.
18 (*a*) P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360. For reviews on the Biginelli reaction, see: (*b*) C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937; (*c*) C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, in press.
19 (*a*) C. O. Kappe and F. S. Falsone, *Synlett*, 1998, 718; (*b*) C. O. Kappe, D. Kumar and R. S. Varma, *Synthesis*, 1999, 1799.
20 H. Kunz and H. Waldmann, *Angew. Chem.*, 1984, **96**, 49.
21 H. Ebiike, K. Maruyyama, Y. Yamazaki, Y. Hirose, K. Kariya, I. Sasaki, Y. Kurono, Y. Terao and K. Achiwa, *Chem. Pharm. Bull.*, 1997, **45**, 863.
22 J. A. Jongejan, J. B. van Tol and J. B. Duine, *Chim. Oggi*, 1994, **12**, 15.
23 W. Krenn, P. Verdino, G. Uray, K. Faber and C. O. Kappe, *Chirality*, 1999, **11**, 659.
24 (*a*) H. Nagai, T. Shiozawa, K. Achiwa and Y. Terao, *Chem. Pharm. Bull.*, 1993, **41**, 1933; (*b*) P. Csomós, L. T. Kanerva, G. Bernáth and F. Fülöp, *Tetrahedron: Asymmetry*, 1996, **7**, 1789; (*c*) S. Oumoch and G. Rousseau, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2841.
25 (*a*) N. K. Yee, L. J. Nummy, D. P. Byrne, L. L. Smith and G. P. Roth, *J. Org. Chem.*, 1998, **63**, 326; (*b*) H. Wakamatsu and Y. Terao, *Chem. Pharm. Bull.*, 1996, **44**, 261; (*c*) H. Nakano, K. Iwasa, Y. Okuyama and H. Hongo, *Tetrahedron: Asymmetry*, 1996, **7**, 2381; (*d*) B. Jouglet and G. Rousseau, *Tetrahedron Lett.*, 1993, **34**, 2307.
26 R. M. de la Casa, J. M. Sánchez-Montero and J. V. Sinisterra, *Biotechnol. Lett.*, 1999, **21**, 123.
27 K. S. Atwal, G. C. Rovnyak, B. C. O'Reilly and J. Schwartz, *J. Org. Chem.*, 1989, **54**, 5898.
28 *cf.* (*a*) D. Mostowicz and M. Chmielewski, *Carbohydr. Res.*, 1994, **257**, 137; (*b*) M. Alpegiani, A. Bedeschi, F. Giudici, E. Perrone, G. Visentin, F. Zarini and G. Franceschi, *Heterocycles*, 1990, **30**, 799.
29 F. Wang, T. Loughlin, T. Dowling, G. Bicker and J. Wyvratt, *J. Chromatogr. A*, 2000, **872**, 279.
30 J. L. L. Rakels, A. J. J. Straathof and J. J. Heijnen, *Enzyme Microb. Technol.*, 1993, **15**, 1051.