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Synthesis and Reactions of Biginelli Compounds -5.[1] Facile Preparation and Resolution of a Stable 5-Dihydropyrimidinecarboxylic Acid.

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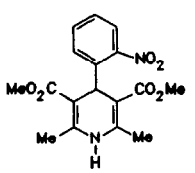
Key Words: Biginelli reaction; dihydropyrimidines; optically pure carboxylic acids; absolute stereochemistry; X-ray analysis.

Abstract: *The synthesis of enantiomerically pure 5-dihydropyrimidinecarboxylic acids* ***7a,b*** *is described. Condensation of benzyl acetoacetate with methylurea and 2-naphthaldehyde gave Biginelli compound* ***3b****, which after methylation and removal of the benzyl group led to racemic acid* ***5b****. Fractional crystallization of diastereomeric α-methylbenzylammonium salts* ***6a,b*** *followed by acidification provided the desired optically pure carboxylic acids* ***7a,b****. Conversion of* ***7a,b*** *to carboxylic acid azides* ***8a,b****, followed by Curtius rearrangement and reaction with 10-undecenol led to chiral urethanes* ***10a,b****. The absolute stereochemistry of acids* ***7a,b*** *was established by X-ray analysis of diastereomeric α-methylbenzylammonium-carboxylate* ***6c****.*

INTRODUCTION

Dihydropyridines (e.g. nifedipine, **1**) represent an important and extensively studied type of calcium channel blockers and much research has been aimed to improve the activity of these compounds and to reduce unwanted side-effects.[2] Recently, this development led to the preparation and pharmacological evaluation[3] of dihydropyrimidines (e.g. **2a**), which, apart from being potent calcium channel blockers, in some cases also show long-lasting antihypertensive activity.[3c,e] These aza analogues of dihydropyridines derive from 3-unsubstituted dihydropyrimidines **2b** (R = H), the so-called Biginelli compounds, which are readily accessible by standard Biginelli condensation[4] or related procedures.[5] In contrast to nifedipine-related dihydropyridines **1**,



1
nifedipine

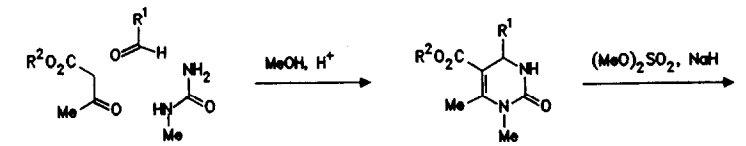
2a R = CO_2Et
2b R = H

dihydropyrimidines **2** are inherently asymmetric and therefore are usually obtained as racemic mixtures. Although first described in 1893,[4a] the chirality of Biginelli compounds **2** was neglected for many decades. Only recently, Atwal et al. has published the first synthesis of enantiomerically pure calcium antagonists of type **2a**.[6] In this article we present a simple and efficient method for the synthesis of both enantiomers of dihydropyrimidine-5-carboxylic acid **5**, and their conversion into N-acyl-substituted 5-aminodihydropyrimidines. The latter type of compounds is of interest as potential chiral receptor in stationary phases, capable of resolving asymmetric nifedipine analogues into their enantiomers.

RESULTS AND DISCUSSION

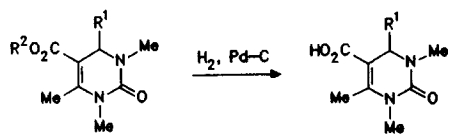
Our first experiments were aimed to find a stereoselective synthesis for Biginelli compounds. Initially we tried to use (*R,R*)-tartaric acid as chiral acidic catalyst in the Biginelli condensation. Although we could not detect any enantioselectivity effect, an equimolar amount of (*R,R*)-tartaric acid was shown to increase the chemical yields significantly, compared to reactions with hydrochloric acid as catalyst.[4] Recently, it was demonstrated that an asymmetric induction can take place at C-4 when chiral aldehydes (deriving from carbohydrates) are employed in the Biginelli condensation.[7] This approach, however, is inapplicable for the synthesis of the desired 4-aryl-dihydropyrimidines. Therefore we studied the effect of a chiral acetoacetic ester in the Biginelli reaction. When (-)-menthyl acetoacetate was treated with 2-naphthaldehyde and 1-methylurea the expected dihydropyrimidine **3a** was obtained as a 1:1 mixture of diastereoisomers, which, although clearly distinguishable by ^{1}H NMR spectroscopy, could not be separated by crystallization or chromatographic techniques.

As alternative to an enantioselective synthesis we tried to resolve racemic dihydropyrimidines into their enantiomers. We envisaged that Biginelli compounds bearing an acidic group such as carboxylic acids **5** could serve as suitable starting materials for this purpose. The synthesis of acids **5b,c** is outlined below. Benzyl acetoacetate was treated with 1-methylurea and an aromatic aldehyde to yield benzyl esters **3b,c**.[8] Methylation with dimethyl sulfate/sodium hydride furnished the N-3 alkylated[9] products **4b,c**, which after hydrogenolyis of the benzyl group[8] gave rise to carboxylic acids **5b,c** in good overall yields.



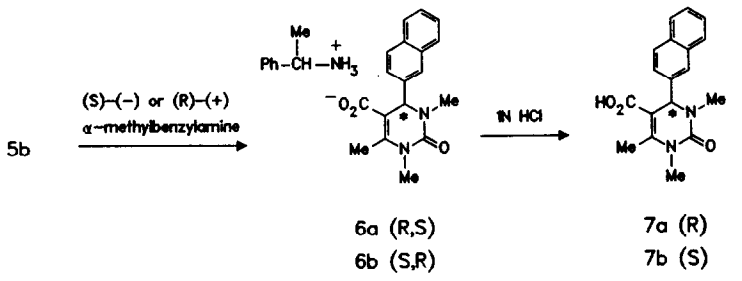
3a–c

3–5	R^1	R^2
a	2-naphthyl	(-)-menthyl
b	2-naphthyl	benzyl
c	phenyl	benzyl



4b,c 5b,c

For the preparation of enantiomers **7a** (*R*) and **7b** (*S*) the racemic naphthyl derivative **5b** was converted into the diastereomeric ammonium salts **6a,b**. Thus treatment of **5b** with (*S*)-(-)-α-methylbenzylamine gave after only one crystallization step 50% of diastereomerically pure (*S,R*) ammonium carboxylate **6a**. Work-up of the mother-liquor with HCl left the enriched (*S*)-acid which on treatment with (*R*)-(+)-α-methylbenzylamine gave 60% of *R,S* ammonium carboxylate **6b**. The diastereomeric salts **6a,b** were cleaved with 1N HCl to yield optically pure carboxylic acids **7a,b** in almost quantitative yield. The enantiomeric excess of **7a** and **7b** (> 96% ee) was determined by ^{1}H NMR analysis using Eu(hfc)$_3$ as chiral shift reagent.



The absolute stereochemistry of **7a** was proven by single-crystal X-ray analysis (Figure 1) of (*R,R*)-α-methylbenzylammonium carboxylate **6c**, from which suitable crystals for X-ray analysis could be obtained. For the phenyl derivative **5c** separation of enantiomers was sluggish and required several crystallization steps. Furthermore we found that the "phenyl acid" **5c** is light-sensitive and slowly decomposes on exposure to light. In contrast, the "naphthyl acids" **5**, **7a,b** are light-insensitive, thermally stable, almost water insoluble and quantitatively recoverable. Therefore these new acids are of interest as chiral auxiliary agents for the separation of chiral amines.

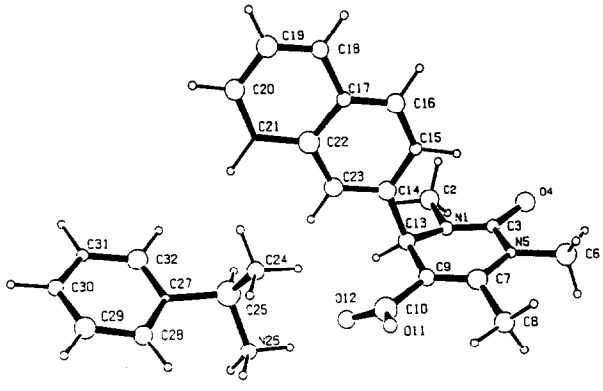
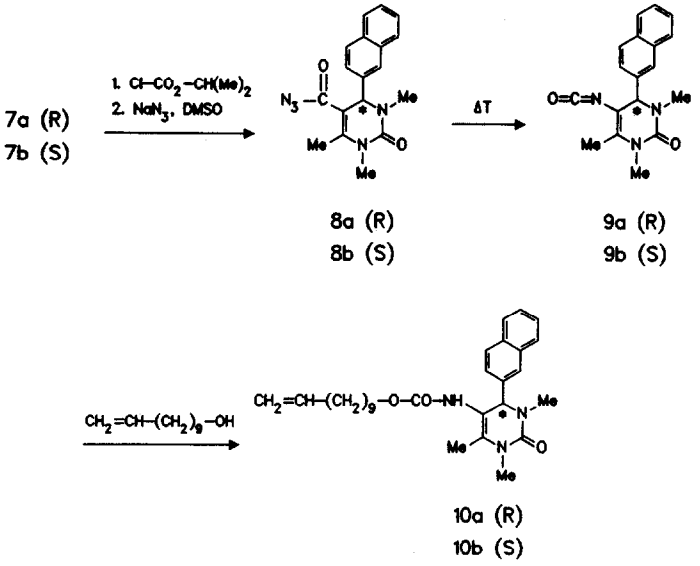


Figure 1. ORTEP-representation of the X-ray structure of **6c**. Non-hydrogen atoms have been drawn at the 50% probability level, hydrogen atoms are drawn as spheres of 0.1 A radius.

In continuation of our work in the field of chiral stationary phases[10] we became interested in the synthesis of 5-aminosubstituted dihydropyrimidines of type **10**, which we expected to be suitable chiral selectors for the separation of asymmetric nifedipine analogues. An entry to these amino derivatives was found by Curtius rearrangement of the corresponding carboxylic acid azides. When acids **7a,b** were reacted with 1-methylethyl chloroformate the corresponding anhydrides were obtained. Although these materials could be isolated, it was most convenient to use the crude anhydrides immediately for the preparation of azides **8a,b** by treatment with sodium azide in DMSO. These carboxylic azides can be stored for several days at 0 °C without decomposition, however, in solution at room temperature slowly eliminate nitrogen to furnish isocyanates **9a,b**. The reaction may be monitored by thin-layer chromatography, IR (2140 cm^{-1} N_3, 2260 cm^{-1} NCO) or ^1H NMR spectroscopy in which a distinctive upfield shift for the C6-methyl group was observed (2.57 in **8b**; vs. 2.02 ppm in **9b**). Urethane derivatives **10a,b** were obtained by reaction of isocyanates **9a,b** with 10-undecenol in refluxing toluene. In order to demonstrate that the reaction sequence **7a,b** → **10a,b** proceeded with retention of optical purity of the products, analytical samples of ethylurethanes **11** were prepared from the racemic (**5b**) and enantiomerically pure (**7a,b**) acids. The optical purity of these urethanes was shown to be higher than 96% ee as judged by HPLC analysis on a chiral stationary phase containing (*S,S*)-N-(3,5-dinitrobenzoyl)-1,2-diphenyl-1,2-diaminoethane as chiral selector.[10]



In conclusion, we have shown that enantiomerically pure 5-pyrimidinecarboxylic acids **7a,b** can be prepared in a simple way from readily available Biginelli compounds **3**, involving resolution of enantiomers by fractional crystallization of diastereomeric ammonium salts. This new access to chiral dihydropyrimidines may prove to be useful for the synthesis of optically pure antihypertensive agents. A particulary attractive feature of the chiral acids **7a,b** is their utility for the preparation of hitherto scarcely reported[11] class of 5-aminodihydropyrimidines (e.g. **10**). This type of compounds will be futher explored for their use in the development of chiral stationary phases and results reported elsewhere.

EXPERIMENTAL SECTION

All melting points were taken on a Gallenkamp melting point apparatus Mod. MFB-595 and are uncorrected. The infrared spectra were recorded with a Perkin Elmer 298 spectrophotometer in KBr pellets. ^{1}H NMR spectra were measured on a Varian EM 360 (60 MHz) and, in special cases on a Varian XL-200 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained with a Varian MAT 111 (80 eV) and microanalyses were performed on a C,H,N-automat Carlo Erba 1106. Optical rotations were measured on a Perkin Elmer polarometer 441 in a 10 cm cell at 20 ± 2 °C. Thin-layer chromatography was done on Merck silica gel aluminium sheets (Kieselgel 60 F_{254}).

4(R,S)-1,2,3,4-Tetrahydro-1,6-dimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid 1-[[1S[1a,2a,5b]]--5-methyl-2-(1-methylethyl)cyclohexyl] Ester (3a). A mixture containing (-)-3-oxobutanoic acid menthyl ester [12] (8.00 g, 33.3 mmol), 2-naphthaldehyde (4.40 g, 28.2 mmol), N-methylurea (3.50 g, 47.2 mmol), and (*R,R*)-tartaric acid (5.00 g, 33.3 mmol) in methanol (25 mL) was heated at reflux for 20 h. After cooling to ambient temperature for 2 h, the crystalline product was filtered, washed with cold ethanol (30 mL) and recrystallized from ethanol to yield a colorless solid **3a** (6.40 g, 53 %): mp 150 °C; IR (KBr) 3220, 1700, 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.20 and 0.30 (d, J = 8 Hz, 3 H), 0.70 and 0.84 (dd, J = 8 Hz, 6 H), 0.50 - 2.04 (m, 9 H), 2.44 and 2.56 (s, 3 H), 3.17 (s, 3 H), 4.50 - 4.75 (m, 1 H), 5.45 and 5.50 (d, J = 3 Hz, 1 H), 6.30 and 6.45 (d, J = 3 Hz, 1 H), 7.20 - 7.85 (m, 7 H), 2 diastereoisomers, 1:1. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.44. Found: C, 74.75; H, 7.82; N, 6.40.

1,2,3,4-Tetrahydro-1,6-dimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid Benzylester (3b). A solution of 3-oxobutanoic acid benzylester (3.84 g, 20.0 mmol), N-methylurea (1.48 g, 20 mmol), 2-naphthaldehyde (2.34 g, 15 mmol), and *R,R*-tartaric acid (3.45 g, 23 mmol) in methanol (10 mL) was heated under reflux for 6 h. After standing overnight at room temperature the preciptated solid was filtered to yield **3b** (4.05 g, 70 %). An analytical sample was prepared by recrystallization from dioxane: mp 150 °C; IR (KBr) 3210, 1710, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 3.15 (s, 3 H), 4.93 (s, 2 H), 5.38 (d, J = 3 Hz, 1 H), 6.12 (d, J = 3 Hz, 1 H), 7.09 (m, 5 H), 7.01 - 7.75 (m, 7 H); mass spectrum (EI), *m/z* (relative intensity) 386 (M^+, 55), 295 (100), 259 (90), 251 (50), 199 (60). Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.65; H, 5.65; N, 7.24.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid Benzyl Ester (4b). To a suspension of **3b** (19.32 g, 50 mmol), and dimethyl sulfate (23.00 g, 180 mmol) in dry toluene (500 mL), sodium hydride (60 % in mineral oil, 2.00 g, 50 mmol) was added in small portions with stirring at room temperature. The reaction mixture was heated to 60 °C, and after all starting material had dissolved (1 h), another portion of **3b** (19.32 g, 50 mmol) and sodium hydride (2.00 g, 50 mmol) were added successively to the reaction mixture. After stirring for one hr at 60 °C the progress of the reaction was monitored by TLC [silica gel, toluene/acetone (3:1), **3b**: R_f = 0.40, **4b**: R_f = 0.55]. After completion of the reaction the mixture was poured into ice/water (300 mL) and neutralized with 2 N hydrochloric acid. The organic phase was separated, washed with water, dried over magnesium sulfate and evaporated. The resulting crude product was digested with hexane, filtered, and washed with a small amount of cold ethanol to give pure **4b** (36.0 g, 89 %). An analytical sample was obtained by recrystallization from ethanol: mp 133 °C; IR (KBr) 1700, 1665, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3 H), 2.88 (s, 3 H), 3.20 (s, 3 H), 5.11 (s, 2 H), 5.39 (s, 1 H), 7.20 (m, 5 H), 7.05 - 7.75 (m, 7 H). Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 74.98; H, 5.90; N, 6.92.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-2-oxo-4-phenyl-5-pyrimidinecarboxylic Acid Benzyl Ester (4c). This compound was prepared from (**3c**) [9] in 85 % yield by the same procedure as described for **4b**:

mp 85 -87 °C (methanol): IR (KBr) 1700, 1655, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.84 (s, 3 H), 3.26 (s, 3 H), 5.08 (s, 2 H), 5.21 (s, 1 H), 7.18 (s, 5 H), 7.25 (s, 5 H). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.32; N, 7.99. Found: C, 71.96; H, 6.20; N, 7.96.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid (5b). A solution of **4b** (36.05 g, 90 mmol) in methanol (250 mL) was added to 10% Pd/C which was previously moistened with toluene (30 mL); (**Caution**: A mixture of dry catalyst with vapors of methanol is inflammable very easily). After triethylamine (9.09 g, 90 mmol) was added, the reaction mixture was hydrogenated for 3 h at room temperature (3 bar H_2 pressure). The solution was filtered from the catalyst, evaporated, and the resulting residue digested with ether. The free carboxylic acid was obtained by treatment with 2 N hydrochloric acid (100 mL). The crude acid was washed with water, dried, and recrystallized from 96% ethanol (250 mL) to yield **5b** (20.0 g, 72%): mp 171 °C (dec.). Concentration of the mother liquor provided an additional amount of less pure **5b** (2.3 g, 8 %); IR (KBr) 3200-3000, 1680, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.94 (s, 3 H), 3.23 (s, 3 H), 5.37 (s, 1 H), 7.17 - 7.87 (m, 7 H), 10.91 (br, 1 H). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.52; H, 5.95; N, 8.89.

1,2,3,4-Tetrahydro-1,3,6-trimethyl-2-oxo-4-phenyl-5-pyrimidinecarboxylic Acid (5c). This compound was prepared in 82 % yield by the same procedure as described for **5b**: mp 165 °C (dec.); IR (KBr) 3200-3000, 1680, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3 H), 2.92 (s, 3 H), 3.24 (s, 3 H), 5.21 (s, 1 H), 7.22 (s, 5 H), 10.30 (br, 1 H). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.90; H, 5.99; N, 10.72.

(4R)-1,2,3,4-Tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid (7a). To a suspension of **5b** (14.50 g, 46.7 mmol) in methanol (95 mL) was added (*S*)-(-)-α-methylbenzylamine (5.66 g, 46.7 mmol) at 40 °C. From the immediatly formed clear solution a colorless solid precipitated upon standing at room temperature, which was filtered after 0.5 h and washed with methanol (3 x 5 mL). This precipitate was heated up to boil with methanol twice (85 and 75 mL) and again was filtered after standing at room temperature for 0.5 h to yield [1(*S*),4*R*]-[(1-phenylethyl)ammonium]-1,2,3,4-tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylate (**6a**) (5.30 g, 53 %): mp 182 - 183 °C, $[\alpha]_{546}$ -76.1 (c = 1, methanol). Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.19; H, 6.76; N, 9.73. A suspension of powdered **6a** (5.00 g, 11.6 mmol) in water (50 mL) was treated with 1 N hydrochloric acid (20 mL). After the addition was finished, the reaction mixture was stirred intensively for several min and then filtered. The precipitate was carefully washed with 1 N hydrochloric acid (5 mL) and several portions of water to give **7a** (3.50 g, 97%). An analytical sample was obtained by recrystallization from ethanol: mp 175 -176 °C (dec.); $[\alpha]_{546}$ = -126.0 (c = 1, dioxane).

(4S)-1,2,3,4-Tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid (7b). The combined methanolic filtrates (cf. preparation of **6a**) were evaporated and the residue digested with ether and filtered. From this crude salt (ca. 13 g) the enriched free *S*-(+)-acid was isolated as described above for **7a** and recrystallized once from ethanol. This material (ca. 8 g) was dissolved in methanol (55 mL) and treated with with (*R*)-(+)-α-methylbenzylamine (3.12 g, 25.7 mmol). Work up as described for **6a** yielded [1(*R*),4*S*]-[(1-phenylethyl)ammonium]-1,2,3,4-tetrahydro--1,3,6-trimethyl4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylate (**6b**) (6.0 g, 60 %): mp 183 °C; $[\alpha]_{546}$ = +76.4 (c = 1, methanol). Treatment of this salt with hydrochloric acid as described above for **7a** yielded **7b** (96 %): mp 175-176°C (dec.); $[\alpha]_D$ = +127.0 (c = 1, dioxane).

[1(R),4R]-[(1-Phenylethyl)ammonium] [1,2,3,4-tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylate] (6c). Optically pure **7a** (230 mg, 0.74 mmol) and (*R*)-(+)-α-methylbenzylamine (90 mg, 74 mmol) were dissolved in hot ethanol. The salt precipitates after cooling and is again recrystallized from ethanol to give pure **7c**: mp 172 °C (dec.). Crystals suitable for X-ray analysis were grown from a solution of the salt in water.

(4S)-1,2,3,4-Tetrahydro-1,3,6-trimethyl-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid Azide (8b). To a solution of **7b** (8.00 g, 25.8 mmol) and triethylamine (4.34 g, 43.0 mmol) in dry acetone (80 mL), freshly distilled 1-methylethyl chloroformate (5.30 g, 43.0 mmol) dissolved in acetone (30 mL) was added at 0 °C over a period of 15 min. After the reaction was completed [TLC, silica gel, toluene/acetone (3:1), **7b**: R_f = 0.10, **8b**: R_f = 0.65], the reaction mixture was poured into ice/water (300 mL), and the product immediately extracted with portions of dichloromethane (150 and 50 mL). The combined organic solutions were washed with cold water (80 mL), dried over magnesium sulfate, and then were evaporated to leave an oil which partly crystallized on treatment with petroleum ether to yield 10 g of crude anhydride [IR (KBr) 1790, 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 7 Hz, 6 H), 2.54 (s, 3 H), 2.98 (s, 3 H), 3.35 (s, 3 H), 4.47 (q, J = 7 Hz, 1 H), 5.33 (s, 1 H), 7.19 - 7.92 (m, 7 H)]. The anhydride was used immediatly without any further purification. Thus, a solution of the anhydride (10 g, 25 mmol) in dry DMSO (10 mL) was poured into a solution of sodium azide (2.90 g, 44.6 mmol) in DMSO (100 mL). The mixture was allowed to stir at room temperature for 15 min, then poured into ice/water (300 mL) and extracted with ether (3 x 150 mL). The combined organic solutions were washed with water (5 x 100 mL), dried over magnesium sulfate and evaporated to yield crystalline **8b** (5.70 g, 66%): mp 55 °C (dec.); $[\alpha]_{546}$ = +73.3 (c = 0.86, dichloromethane); IR (KBr) 2140, 1680, 1660, 1600 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.57 (s, 3 H), 2.96 (s, 3 H), 3.31 (s, 3 H), 5.33 (s, 1 H), 7.19-7.94 (m, 7 H).

(4R)-1,2,3,4-Tetrahydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-pyrimidinecarboxylic Acid Azide (8a). Using the procedure described for **8b**, **7a** was converted into **8a** (68 %): mp 55 °C (dec.), $[\alpha]_{546}$ = -72.8 (c = 0.9, dichloromethane).

(4S)-3,4-Dihydro-5-isocyanato-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-1H-pyrimidin-2-one (9b). A solution of **8b** in dry toluene was heated under reflux for 0.5 h. The reaction was conveniently followed by TLC [silica gel, dichloromethane/acetone (4:1), **8b**: R_f = 0.95, **9b**: R_f = 0.90]. Evaporation of the solvent yielded quantitatively **9b** as yellow oil: $[\alpha]_D$ = -302.0 (c = 0.80, dichloromethane); IR (neat) 2260, 1650 cm^{-1}; ^1H NMR ($CDCl_3$): 2.02 (s, 3 H), 2.70 (s, 3 H), 3.23 (s, 3 H), 4.88 (s, 1 H), 7.21 - 8.05 (m, 7 H).

(4R)-3,4-Dihydro-5-isocyanato-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-1H-pyrimidin-2-one (9a). Using the procedure described for **9b**, **8a** was converted quantitatevly to **9a**, yellow oil: $[\alpha]_{546}$ +298.0 (c = 0.90, dichloromethane).

(4S)-3,4-Dihydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-[(10-undecenyloxy)carbonyl]amino-1H-pyrimidin-2-one (10b). A solution of **9b** (4.00 g, 13 mmol), and 10-undecenol (2.21 g, 13 mmol) in dry toluene (30 mL) was refluxed for 3 h. The progress of the reaction was followed by TLC [silica gel, dichloromethane/acetone (4:1), **9b**: R_f = 0.90, **10b**: R_f = 0.85]. After evaporation of the solvent, the resulting brownish oil was purified by medium-pressure chromatography on silica gel (200 g, 30-60 μ from GRACE, at 3 bar, dichloromethane/acetone 20:1) to yield **10b** (3.0 g, 48 %). An analytical sample was obtained by recrystallization from cyclohexane, mp: 65-66 °C; $[\alpha]_{546}$ = +129.0 (c = 0.70, methanol); IR (KBr): 3180, 1715, 1630 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21, 1.50 (m, 14 H), 1.90 (s, 3 H), 2.00 (m, 2 H), 2.75 (s, 3 H), 3.20 (s, 3 H), 4.05 (m, 2 H), 5.00 (m, 3 H), 5.31 (br, 1 H), 5.72 (m 1 H), 7.30 - 7.90 (m, 7 H). Anal. Calcd for $C_{29}H_{39}N_3O_3$: C, 72.92; H, 8.23; N, 8.80. Found: C, 72.76; H, 8.12; N, 8.74.

(4R)-3,4-Dihydro-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-5-[(10-undecenyloxy)carbonyl]amino-1H-pyrimidin-2-one (10a). Using the procedure described for **10b**, **9a** was converted to **10a** (51 %): mp 64-66 °C; $[\alpha]_{546}$ = -125 (c = 1, methanol).

(4R,S)-3,4-Dihydro-5-[(ethoxycarbonyl)amino]-1,3,6-trimethyl-4-(2-naphthyl)-2-oxo-1H-pyrimidin-2-one (11). A solution of *rac*-**8** (335 mg, 1 mmol) in ethanol (5 mL) was refluxed for 1 h. After evaporation of the solvent, the crude product was recrystallized from ethanol to give **11** (210 mg, 60 %): mp 136 °C; IR (KBr) 3180, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.97 (s, 3 H), 2.93 (s, 3 H), 3.23 (s, 3 H), 4.21 (q, J = 7 Hz, 2 H), 5.10 (br, 1 H), 5.42 (br, 1 H), 7.40

- 8.00 (m, 7 H). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.82; H, 6.66; N, 11.72. Found: C, 67.97; H, 6.56; N, 11.89.

HPLC Analysis: HPLC measurements of *rac* and enantiomerically pure **11** were performed on a chiral stationary phase: Chiral selector: (*S,S*)-N-(3,5-dinitrobenzoyl)-1,2-diphenyl-1,2-diaminoethane,[10] solvent: n-heptane/2-propanol/diethylamine 95/5/0.02; flow 1ml/min, k' = 4.52, α = 1.15. Optical purity of **11**: 96% ee.

X-ray analysis of 6c:[13] Diffraction data were collected on a modified STOE diffractometer at 102(2) K, using graphite monochromated MoK_α radiation (λ = 0.71069 A). Crystals (0.35 x 0.1 x 0.05 mm) were grown from water. Unit cell papameters were obtained by least squares refinement against the setting angles of 11 reflections with 5° < 2Θ < 11°. Crystals are monoclinic, space group $P2_1$, with 2 formula units $C_{26}H_{29}N_3O_3$ (431.5) in the unit cell: a = 11.047(19) A, b = 6.103(11) A, c = 16.206(22) A, ß = 81.40(11)°, V = 1080(1) A^3, d_{calc} = 1.327 g/cm^3. Intensity data (ω-scan, $\Delta\omega$ = 2.4°) were collected for two octants yielding 1702 observed, 1602 unique and 578 significant (F_{obs} > 4σ(F)) structure factors (LP and empirical absorption correction). The structure was solved with direct methods and refined with least squares. The non-hydrogen atoms were refined with isotropic atomic displacement parameters, hydrogen atoms were included at positions calculated on the basis of stereochemical plausibility. The refinement converged at R = 0.107, R_w = 0.087 ($1/\sigma^2$-weights) for 128 parameters and 578 observations.

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