ENANTIOSELECTIVE SYNTHESIS OF β-AMINO ACIDS. 5. STEREOSELECTIVE REACTION OF CHIRAL PYRIMIDINONE ENOLATES WITH ALDEHYDES [1,+]

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Abstract -Hydro-pyrimidinones ((2*S*,6*R*)-**3**) and ((2*S*)-**6**) were prepared from methyl crotonate *via* 3-aminobutanoate, and their corresponding lithium enolate and dienolate derivatives were added to various aldehydes. The high regio- and stereoselectivities observed in these aldol reactions pave the road for the preparation of enantiomerically pure β-hydroxy-β'-amino acids. The structures of the products were confirmed by X-ray crystal structure analysis (eight examples).

INTRODUCTION

As a result of the wide spectrum of applications of α-amino acids, a great deal of attention has been paid to the development of new methodologies for the preparation of both natural and unnatural α-amino acids in enantiopure form.[2-4]

β-Amino acids, although less abundant than their α-analogues, are also present in peptides,[5] and in free form they show interesting pharmacological effects.[6] Furthermore, β-amino acids are synthetic precursors of β-lactams,[7] which are potentially biologically active and of continuous interest.[8] In this respect, a good number of methods for the synthesis of racemic β-amino acids have been developed,[9] but only recently has the preparation of enantiomerically pure derivatives emerged as an important and challenging synthetic endeavor.[10] The procedures developed so far for the enantioselective synthesis of β-amino acids can be divided into seven categories, including:

+ Dedicated to *Arnold Brossi* at the occasion of his 70th birthday.

‡ This paper describes the Diplomarbeit (master's thesis) of P. M., ETH Zürich, 1993.

◊ The eight crystal structures in Fig. 1 were determined by B. R. in the course of the Kristallographie-Praktikum (undergraduate lab course in crystallography), ETH Zürich, 1993; see also acknowledgements.

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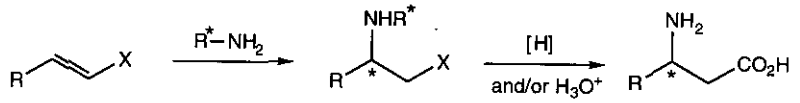
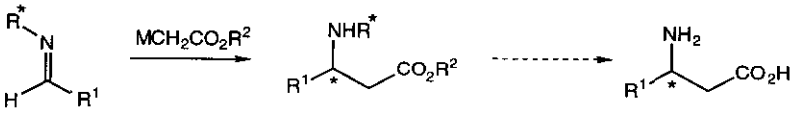
(1) The "chiral pool" method,[11] which refers to the utilization of inexpensive, readily available natural products as substrates to be converted into enantiomerically pure β-amino acids *via* conventional organic synthesis.[12]
(2) Asymmetric addition of amines to α,β-unsaturated esters and nitriles[13] (*Scheme 1*).

Scheme 1



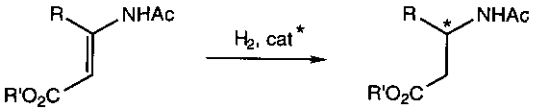
(3) Addition of *C*-nucleophiles to chiral imines[14] (*Scheme 2*).

Scheme 2



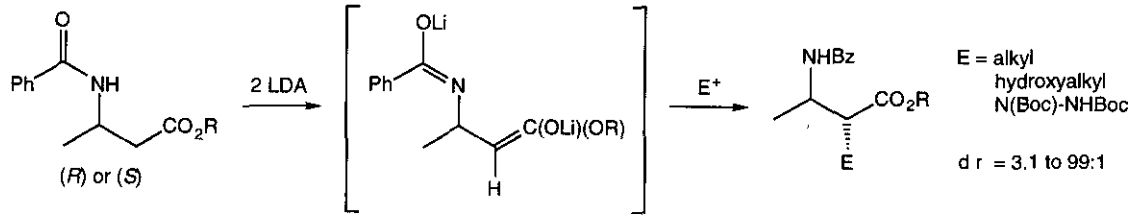
(4) Enantioselective hydrogenation of 3-aminoacrylic acid derivatives[15] (*Scheme 3*).

Scheme 3



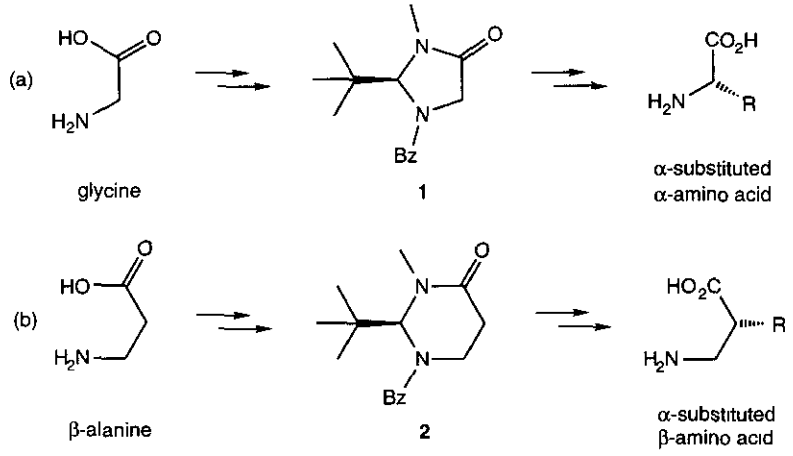
(5) Stereoselective alkylation of β-amino ester or amide enolates. For example, *N*-acyl-β-amino acid derivatives have been doubly deprotonated and then α-alkylated with moderate to excellent selectivity[16] (*Scheme 4*).

Scheme 4



Encouraged by the great potential of imidazolidinone (**1**) for the preparation of (*R*)- or (*S*)-α-amino acids,[17] we decided to explore the usefulness of chiral β-alanine derivative (**2**) as a starting material for the enantioselective synthesis of (*R*)- or (*S*)-β-amino acids.[18] In fact, alkylation of enolate **2**-Li with alkyl halides RX at -75°C took place with high diastereoselectivity (ds = 86-97%) from the side opposite to the *tert*-butyl group to afford the *trans*-products.[19] The hydrolysis of the resulting adducts proceeded with 6 N hydrochloric acid to afford the desired α-substituted β-amino acids in good yields[18,20] (*Scheme 5*).

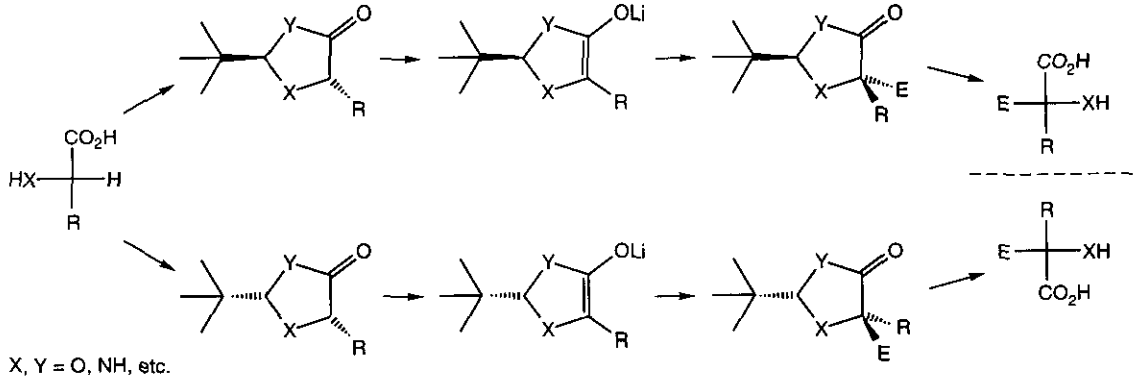
Scheme 5



(6) Self-regeneration of stereogenic centers.

Over a decade ago, Seebach and coworkers carried out transformations in which α-hydroxy and α-amino acids were α-alkylated without racemization and without employing a chiral auxiliary reagent.[17a,21] To this end, the starting acid was first converted to one of two possible diastereoisomeric cyclic acetals with pivalaldehyde, so that a *temporary*, auxiliary stereogenic center was created. Then, an enolate was generated by deprotonation with base: *the original stereogenic center is destroyed* (converted to a trigonal center). In the third step, the reaction of the enolate with an electrophile, the bulky substituent on the acetal center induces the *stereoselective regeneration* of the original center of chirality. Finally, the temporary stereogenic acetal center is removed, affording the new α-branched carboxylic acid in enantiopure or enantioenriched form (*Scheme 6*). An application of this principle to the enantioselective preparation of β-aryl-β-amino acids has recently been described.[22]

Scheme 6

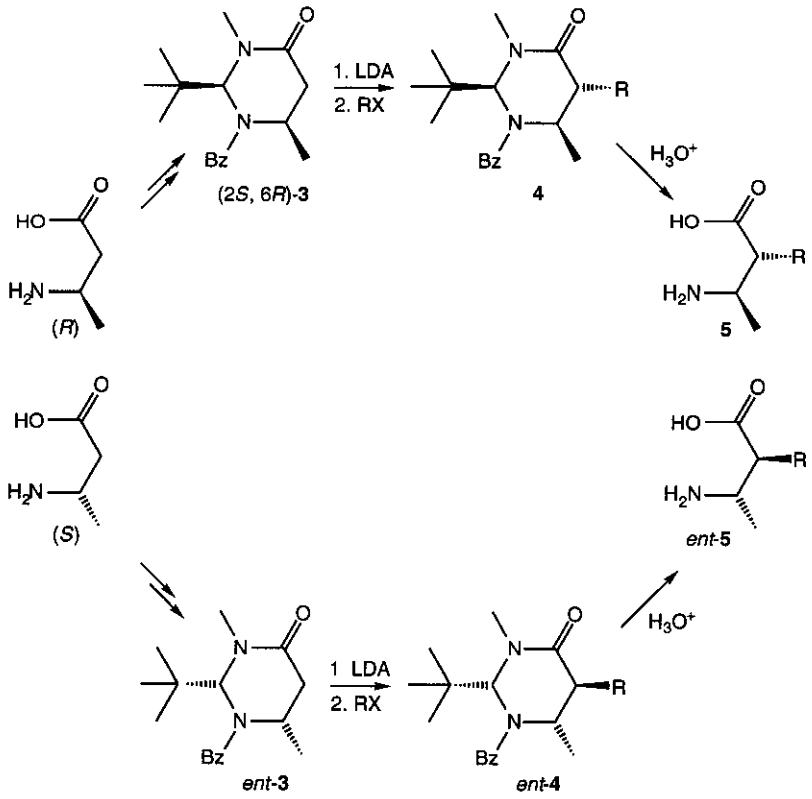


(7) Enzymatic methods. Very recently, several enantiopure β-amino acids have been prepared by routes which involve at one point the enzymatic resolution of racemates.[23]

AIM OF THIS WORK

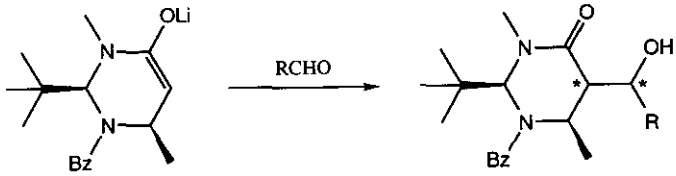
Quite recently, we have reported that enantiopure perhydropyrimidin-4-ones (**3**) and *ent*-**3** (prepared from (*R*)- and (*S*)-3-aminobutanoic acids) can be alkylated with formation of a single diastereoisomer (**4** and *ent*-**4**). Hydrolysis of these 5,6-dialkylperhydropyrimidin-4-ones led to the important α,β-disubstituted β-amino acids (**5**) and *ent*-**5**[24,25] (*Scheme 7*).

Scheme 7



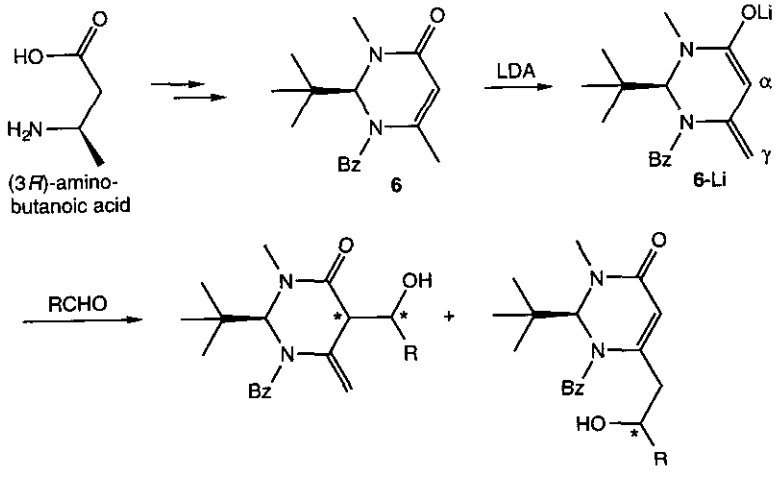
In the present work, we have determined the diastereoselectivity of the aldol addition of enolate **3**-Li to various aldehydes RCHO. The creation of two stereogenic centers in this reaction (*Scheme 8*) could afford up to four diastereoisomeric products.

Scheme 8

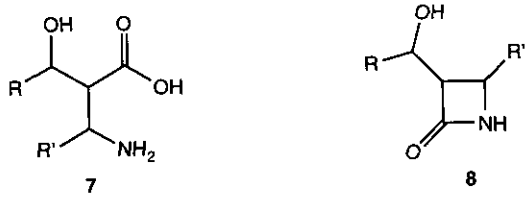


Furthermore, in a new application of the principle of self-regeneration of stereogenic centers (see the Introduction) (*R*)-3-aminobutanoic acid was to be converted to enantiopure (*S*)-1-benzoyl-2-*tert*-butyl-3,6-dimethyldihydropyrimidin-4-one (**6**), the dienolate **6**-Li of which was to be alkylated with methyl iodide and added to aldehydes (*Scheme 9*).

Scheme 9



It should be appreciated that the aldol products arising from α addition (*Schemes 8* and *9*) are potential precursors of enantiopure β-amino-β'-hydroxy acids (**7**) as well as of 1'-hydroxy-β-lactams (**8**), whose importance as antibiotics is well recognized.[26]

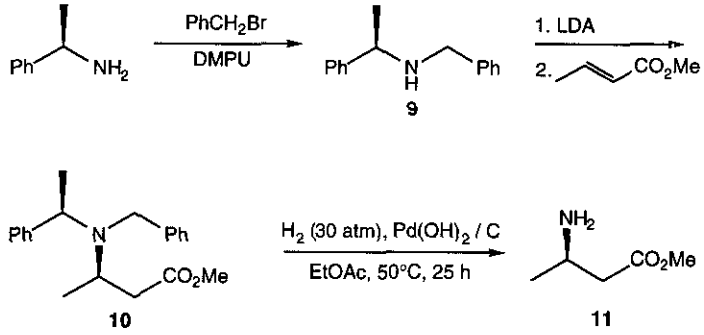


RESULTS AND DISCUSSION

A. Preparation of Methyl (R)-3-Aminobutanoate (11).

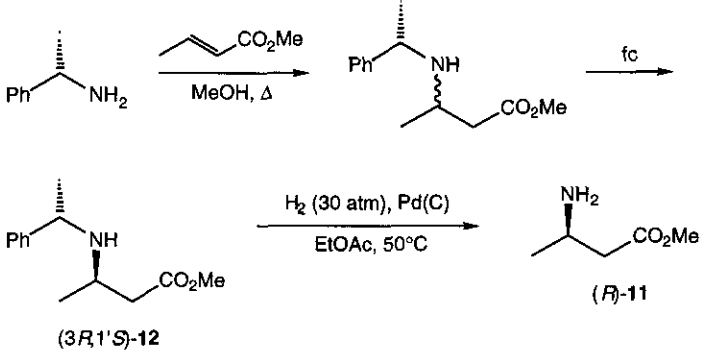
(*R*)-*N*-Benzyl-1-phenylethylamine (**9**) was prepared by monobenzylation of (*R*)-1-phenylethylamine according to the recently described procedure.[27] Following the procedure of Davies and Ichihara,[13e] a *twofold* excess of the lithium amide **9**-Li is used for the Michael-addition to methyl crotonate which occurs in 83% yield and better than 99% diastereoselectivity.[28] However, in our hands, removal of the benzyl and phenethyl groups from adduct (**10**) with Pearlman's catalyst [$Pd(OH)_2$/C] in ethanol[13e] was problematic owing to incomplete hydrogenolysis. Nevertheless, the desired reaction was successful at increased temperature and hydrogen pressure, in ethyl acetate as the solvent[29,30] (*Scheme 10*).

Scheme 10



Because additional difficulties were encountered in the scaling-up (3 → 76 mmol) of the hydrogenolysis step (**10** → **11**), and since we could make good use of *both* enantiomers of the β-amino acid, we resorted to a less stereoselective but practical method for the preparation of ester (**11**). As described previously,[23b,24a] Michael addition of (*S*)-1-phenylethylamine to methyl crotonate gave a 3:2 mixture of (3*R*,1'*S*)- and (3*S*,1'*S*)-**12**, which were separated by flash column chromatography. The hydrogenolytic removal of the phenethyl group was then accomplished by means of palladium on charcoal in solvent ethyl acetate and a hydrogen pressure of 30 atm at 50°C (*Scheme 11*).

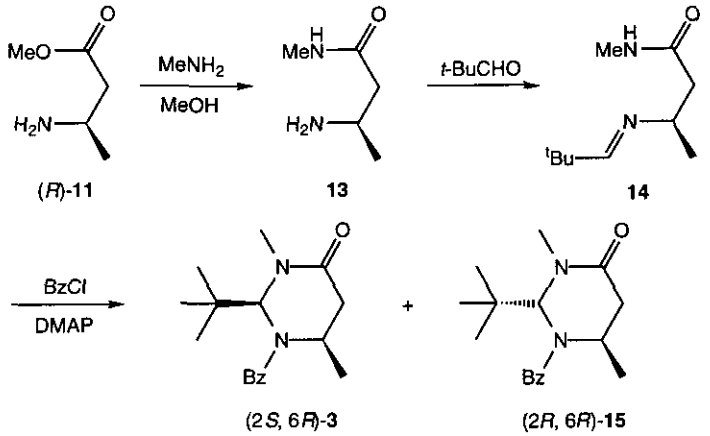
Scheme 11



B. Preparation of Perhydropyrimidinone (2S, 6R)-3.

β-Aminoester (*R*)-**11** was converted in four steps to the enantiomerically pure heterocycle (**3**) according to the previously described procedure[24a] (*Scheme 12*). Thus conversion of (*R*)-**11** to the amide (**13**) was followed by Schiff base formation with pivalaldehyde. Imine (**14**) was then treated with benzoyl chloride/DMAP to afford cyclized heterocycles *cis*-(2*S*, 6*R*)-**3** and the *trans* diastereoisomer (**15**) in a *ca.* 10:1 ratio. Chromatographic separation and recrystallization gave pure **3** in 30% overall yield from **11**[24a] (*Scheme 12*).

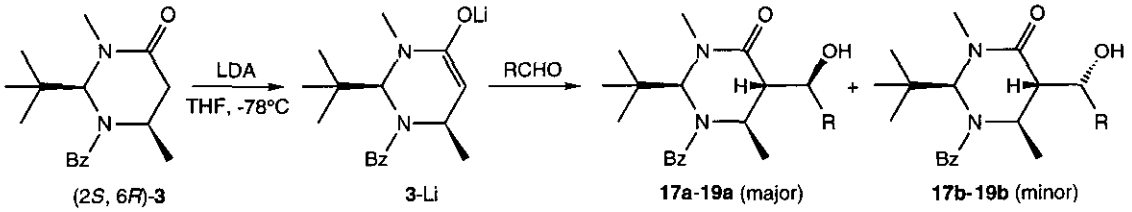
Scheme 12



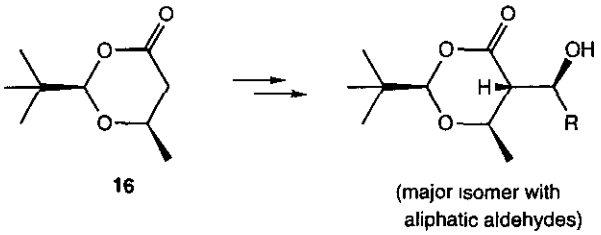
C. Aldol Additions of Pyrimidinone Enolate 3-Li to Aldehydes.

In analogy to aldol reactions involving (*R,R*)-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one (**16**) with aliphatic or aromatic aldehydes,[31] Li enolates of (2*S*, 6*R*)-**3** (in THF at -78°C) were treated with 1.3 - 2.1 equivalents of aldehyde, and then the reaction mixture was quenched with saturated aqueous ammonium chloride solution (*Scheme 13*).

Scheme 13



(specification of R see *Table 1*)



In all cases, only two diastereoisomeric products were observed, out of four possible stereoisomers. The ratios of these major:minor products (*Table 1*) were determined from the crude reaction mixture by ^{13}C-Nmr spectroscopy; in particular, by integration of the well resolved C(1')-carbon signals. Because the alkylation of **3**-Li has been found to give exclusively the product arising from addition *trans* to the *tert*-butyl group,[24a] the configuration shown in Scheme 13 was tentatively assigned to aldol products (**17a** - **19a**), and subsequently confirmed by single-crystal X-ray structural determination (see *Section G*) of **17a** and **18a**. On the other hand, the configuration of **19a** was correlated with that of **17a** and **18a** by comparison of chemical shifts and coupling constants in their ^{1}H-Nmr spectra.[32]

Table 1. *Aldol Additions of the Enolate (2S,6R)-3-Li.*

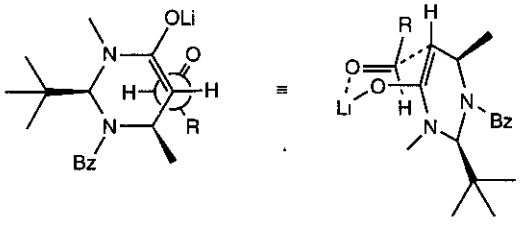
R	Products	Epimer ratio **a : b**	Yield[a] [%]
Phenyl	**17**	2.2 : 1	57
Isopropyl	**18**	4 : 1	51
Methyl	**19**	7 : 2	58

[a] Referring to the major diastereoisomer after purification.

As summarized in Table 1, addition of **3**-Li to both aliphatic and aromatic aldehydes occurs with very high stereoselectivity at the enolate's α carbon (ds > 98%). Apparently, the steric hindrance generated by the axial *tert*-butyl and the C(6)-methyl groups is overwhelming, so that C-C bond formation takes place exclusively from the enolate face opposite to these substituents (the *Re* face).[19,24a]

With regard to the relative topicity with which the trigonal faces of the enolate **3**-Li and the aldehydes prefer to approach each other, the configuration at C(1') in **17a** - **19a** indicates that it is *like* (*lk*, *Re*/*Re*)[33] (*Scheme 14*), as in the additions of the dioxanone analogue to aliphatic aldehydes.[31,34]

Scheme 14

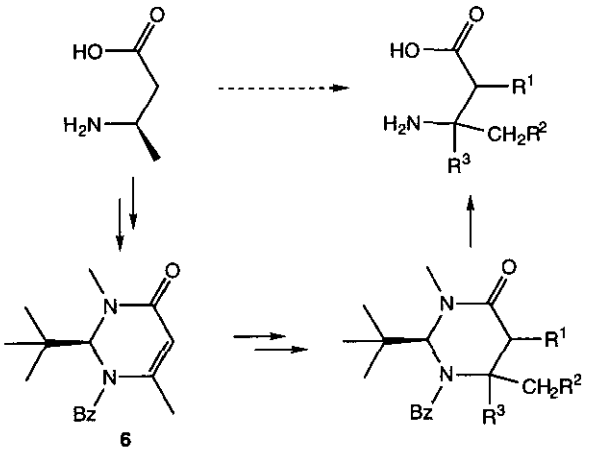


D. Preparation of the α,β-Unsaturated Pyrimidinone (S)-6.

(*S*)-1-Benzoyl-2-*tert*-butyl-3,6-dimethyldihydropyrimidin-4-one (**6**) could be (as is the case with the dioxinone analogue[35]) a versatile substrate in [2 + 2] cycloadditions, Michael additions, electrophilic and/or nucleophilic

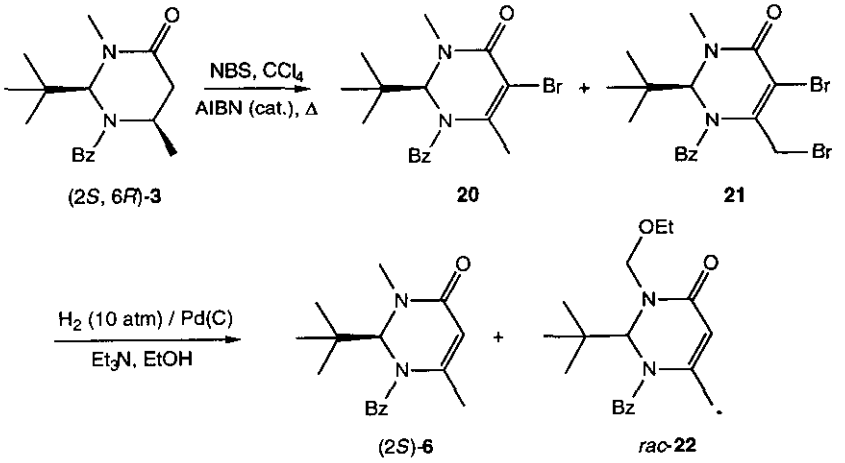
substitutions, etc. As indicated in the introduction, a variety of α,β-substituted β-amino acids may be produced in a further application of the principle of "self-regeneration of stereogenic centers"[17,19,21] (*Scheme 15*).

Scheme 15



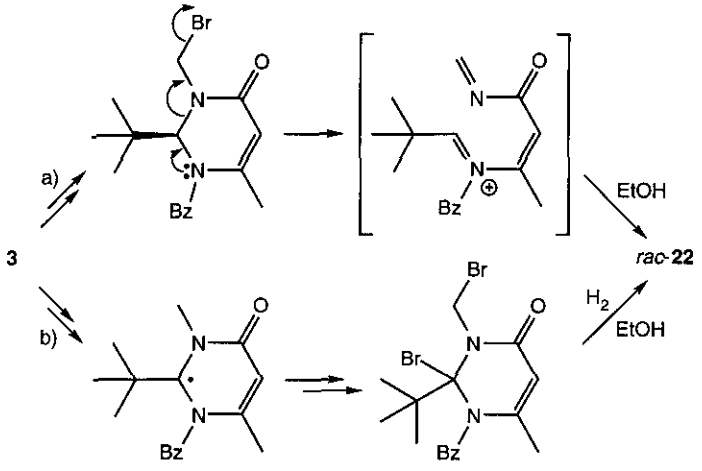
Access to enantiopure (*S*)-**6** was achieved *via* radical bromination of the saturated precursor (2*S*, 6*R*)-**3**, which afforded a ca. 2:1 mixture of the monobromide (**20**) and the dibromide (**21**).[36] This mixture was reduced with hydrogen (palladium/C catalyst) to give the desired product (**6**) in 55 - 60% yield over the two steps (*Scheme 16*).

Scheme 16



In addition to the expected, enantiomerically pure product (**6**), which has a characteristic high value[18b,22b] of optical rotation $[\alpha]_D = +442.7°$ (c = 1.01, $CHCl_3$), *ca.* 10% yield of a racemic byproduct was isolated, and characterized as **22** (*Scheme 16* and *Section G*). Scheme 17 presents two possible mechanisms (a) and (b) for the formation of racemic **22**.

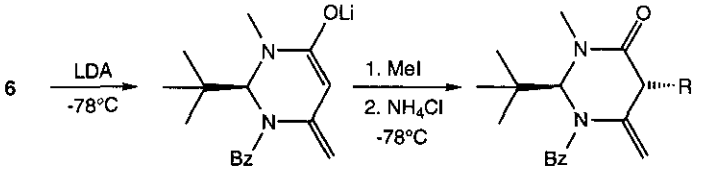
Scheme 17



E. Regio- and Stereoselectivity of the Reaction of Dienolate (S)-6-Li with Methyl Iodide.

Conjugated pyrimidinone (**6**) was deprotonated with lithium diisopropylamide (LDA) in THF at -78°C, and the resulting dienolate **6**-Li was treated with methyl iodide at -78°C. This reaction could in principle afford the product of an electrophilic attack at the endocyclic 2-position and/or at the exocyclic 4-position of the dienolate, as mixtures of the corresponding stereoisomers. However, only the product of the reaction at the endocyclic position was observed as a single diastereoisomer (ds > 98%) in 37% yield (**23**, *Scheme 18*). The assignment of the *trans* configuration in **23** was achieved by single-crystal X-ray structural analysis (see *Section G*). The second product, formed in 35% yield, was identified as the isomer (**24**) of the starting material, which apparently arose from simple α-protonation of the dienolate **6**-Li[37] (*Scheme 18*).

Scheme 18



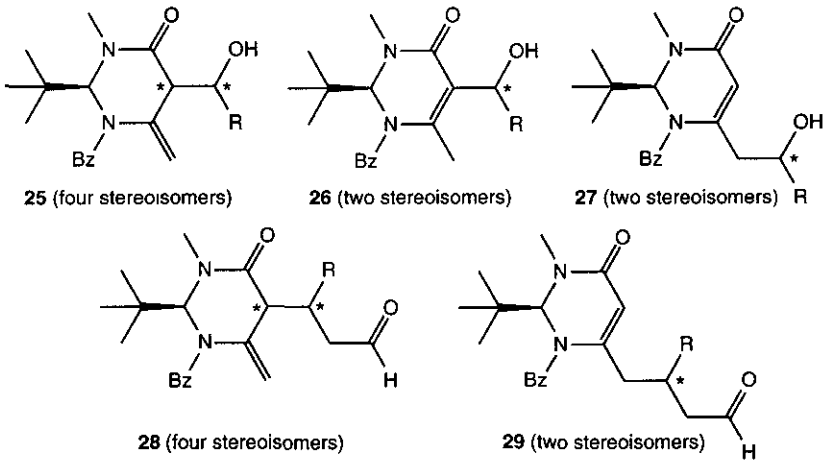
(2*S*)-**6**-Li

23, R = Me
24, R = H

F. Regio- and Stereoselectivity of the Reaction of Dienolate (S)-6-Li with Aldehydes.

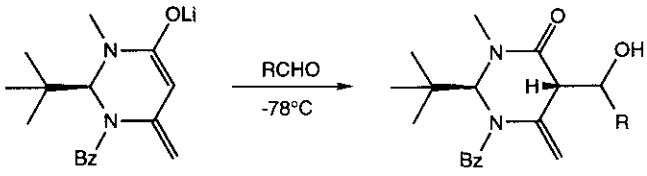
The aldol reaction of dienolate **6**-Li with aliphatic and aromatic aldehydes can in principle again proceed at the *endo-* or *exocyclic* position of the dienolate and, depending on the final position of the double bond, up to eight regio- and diastereoisomeric products may be formed (see **25** - **27** in *Scheme 19*). Furthermore, in the case of α,β-unsaturated aldehydes, the enolate addition may proceed in a Michael-fashion (see **28** and **29** in *Scheme 19*).

Scheme 19



In the actual experiment, **6**-Li was generated with lithium-hexamethyldisilazide (LHMDS) (the use of LDA in these aldol reactions led to lower yields due to the formation of several side products), and addition of the aldehydes at -78°C gave the results summarized in Table 2. It can be appreciated that with all aldehydes studied only the products of addition at the endocyclic carbon were observed.

Table 2. *Aldol Reactions of Dienolate 6-Li.*

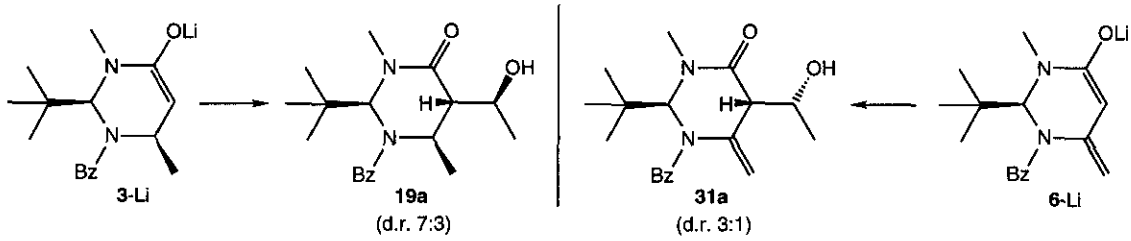


R	Products	Ratio of diastereo-isomers (d.r.)	Yield[b] [%]
Phenyl	**30**	>50 : 1[a]	82
Methyl	**31**	3 : 1	78
trans-CH=CHMe	**32**	>50 : 1[a]	56

[a] No minor diastereoisomer was detected by ^{1}H-Nmr spectroscopy
[b] After flash chromatography.

As was the case in the aldol reactions of the saturated analogue **3**-Li, only the products of *trans* addition were observed. The assignment of the configuration of both the major and minor diastereoisomeric product (**31a**) and (**31b**) was secured from the X-ray crystallographic analysis of both isomers (see *Section G*). The most surprising result is the fact that the configuration at C(1') in the major isomer obtained with the dienolate is opposite to that observed with the saturated heterocycle (*Scheme 20*)!

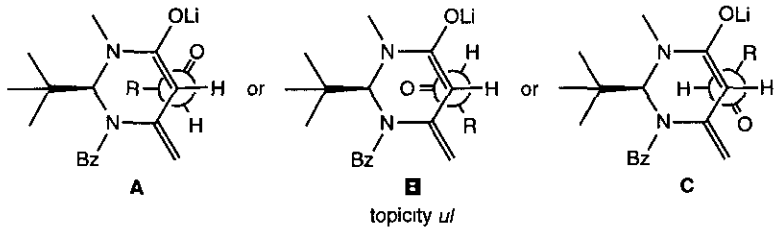
Scheme 20



The aldol additions with benzaldehyde and crotonaldehyde to give **30** and **32** proceed with the same stereochemical preference. This could be established by ^{13}C-Nmr spectroscopic correlation of the main diastereoisomeric products (**30a**) and (**32a**) with **31a**. In particular, the similar chemical shifts for C(5) and C(6) in **31a** and **32a** support the assignment of the C(1') configuration for the latter. Thus, it is concluded that the aldol additions of **6**-Li are completely regioselective, and proceed exclusively from the enolate face opposite to the *tert*-butyl group (the *Re* face). Furthermore, with benzaldehyde and crotonaldehyde the diastereoselectivity of the reaction is essentially complete, to afford the aldol products originating from a relative topicity *unlike* in the coupling step (*Scheme 21*). These results provide further manifestation of dramatic stereoselectivity induced by remote stereogenic centers.[38] It is interesting to note that reversal of the stereochemical course of reaction when going from aliphatic to aromatic aldehyde substrates is opposite to the situation encountered with dioxanone enolates; they give much higher selectivity with aliphatic and no or poor selectivity with aromatic aldehydes.[34]

Since we favor the approach trajectory **A** in which Li binds to both oxygens, as shown in Scheme 21, with the R group underneath the heterocyclic ring, this special behaviour of aromatic aldehydes may have to do with a charge-transfer interaction between the π-systems of the aldehyde (acceptor) and that of the dienolate (super-donor containing *two* enamine and an enolate moiety!).

Scheme 21

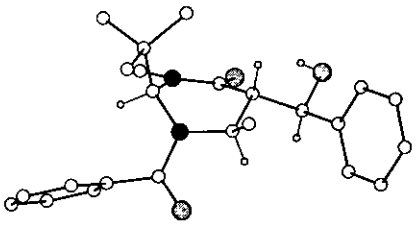


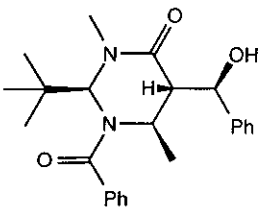
G. X-Ray Crystallographic Structure Determinations

The assignment of the configurations of the aldol products obtained in this work is complicated by serious broadening of the ^{1}H- and ^{13}C-Nmr signals due to dynamic conformational phenomena which provoke near coalescence of most signals at ambient temperature. Spectra with sharper signals could be obtained at 100°C (DMSO-d_6), but configurational assignments based exclusively on Nmr data are never really safe, so we decided to determine the crystal structures of several pyrimidinone derivatives described herein.

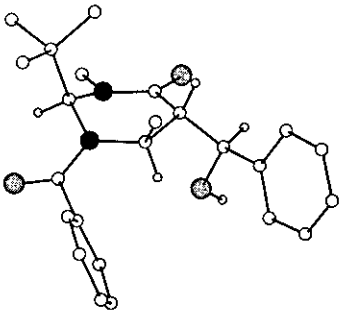
We succeeded in preparing suitable single crystals of the six aldol products (**17a**, **17b**, **18a**, **18b**, **31a**, and **31b**), as well as of the pyrimidinone derivatives (*rac*-**22** and (2*S*, 5*R*)-**23**). The X-ray crystal structures are shown in Figure 1.[43]

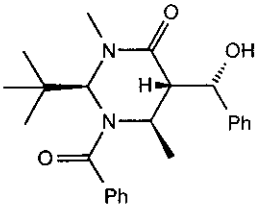
Figure 1. *X-Ray Crystal Structures of Eight Pyrimidinone Derivatives. For Puckering Parameters, Pyramidalisations of the Amide Nitrogen Atoms and Crystal Data see Tables 3, 4, and 6, respectively.*



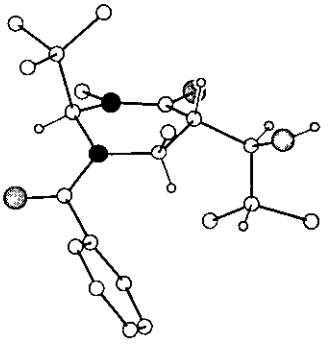


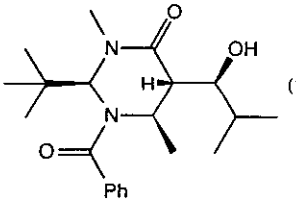
(1'*R*)-**17a**



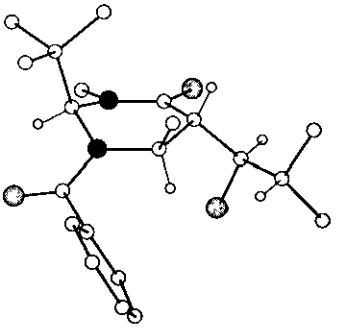


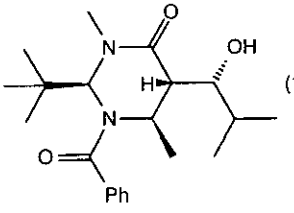
(1'*S*)-**17b**





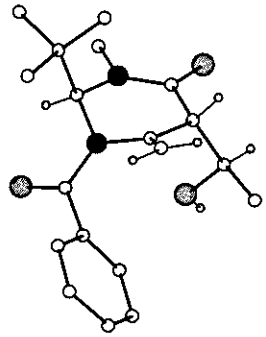
(1'*S*)-**18a**

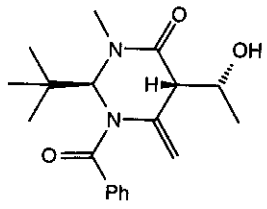




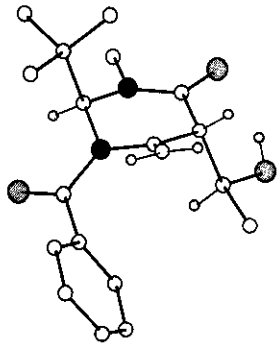
(1'*R*)-**18b**

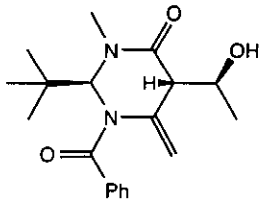
Figure 1 (cont.)



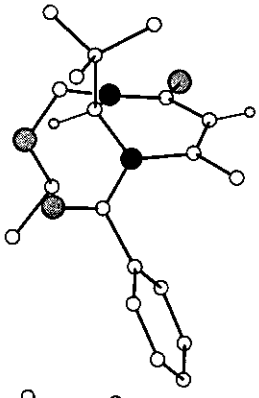


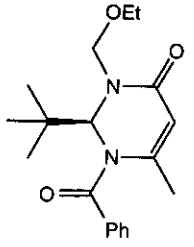
(1'*R*)-**31a**



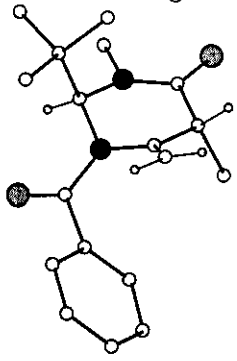


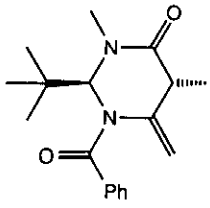
(1'*S*)-**31b**





rac-**22**





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The amide segments in these heterocycles preclude chair conformations with equatorial *tert*-butyl groups for these six-membered rings, which rather adopt sofa- or twist-boat-like arrangements (see below). Nevertheless, a most interesting feature is the *quasi*-axial orientation of the *tert*-butyl group in all compounds.[19,22] The origin of this conformational feature is the $A^{1,3}$-effect exerted by the amide groups:[39] the energy required to rotate an amide bond all the way out of conjugation is 15 - 20 kcal/mol, much larger than the conformational steric repulsion originating (in our system) from the axial arrangement of the *tert*-butyl substituent. All but one (**17a**) pyrimidinone derivatives of which we have crystal structures (in total 13!) have the 1-benzoyl C=O group pointing towards the *tert*-butyl substituted acetal center C(2).

Of course, the structural data presented in Figure 1 permit a safe assignment of the relative configurations of the stereogenic centers created during aldol additions and alkylations (see *Sections C, E,* and *F*). Since the absolute configuration of (+)-(*R*)-aminobutanoic acid used throughout this investigation has been safely assigned (see references[16]), all structures in Figure 1 show the correct relative and absolute configurations.

Analysis of the X-ray crystallographic data allows also the proper definition of the six-membered ring conformation, in particular by determination of the so-called puckering parameters.[40] In Table 3, we have collected the values of the pertinent puckering parameters and the appropriate characterization of the ring form.

Table 3. *Puckering Parameters and Ring Shape Characterization*[40] *in* ***17, 18, 22, 23 and 31.***

Structure	q_2	q_3	φ [°]	Θ [°]	Ring shape
17a	0.548	-0.039	220.86	-85.93	twist[a]-boat
17b	0.337	0.136	49.93	68.02	twist[a]-sofa
18a	0.428	-0.116	226.91	-74.84	twist[a]-boat
18b	0.335	0.141	47.51	67.17	twist[a]-sofa
22	0.411	0.157	41.54	69.09	twist[a]-sofa
23	0.222	-0.338	174.89	-33.30	sofa[b]
31a	0.312	-0.269	178.49	-49.23	sofa

a) Not very pronounced twisting.
b) More sofa than chair.

In contrast to five-membered ring analogues,[19,41] the endo- and exocyclic amide moieties of the pyrimidinones described here are only slightly pyramidalized (compare the Δ values for pyramidalization in *Table 4*).

Table 4. *Sums of Bond Angles and Pyramidalizations Δ on Amide N-Atoms in Pyrimidinones(**17**, **18**, **22**, **23** and **31**).*

Structure	Σ α endo	Δ endo [Å]	Σ α exo	Δ exo [Å]	τ_1[a)]	τ_2[b)]
17a	359.6	0.10	359.7	0.09	-178.6	118.2
17b	360.0	0.05	359.9	0.06	0.9	10.2
18a	360.0	0.01	359.9	0.02	-0.7	1.6
18b	360.0	0.01	359.6	0.05	1.9	5.2
22	359.5	0.08	359.0	0.06	-19.9	-13.9
23	359.4	0.06	359.7	0.04	3.0	-3.5
31a	360.0	0.01	359.9	0.02	-1.0	8.4
31b	359.6	0.05	359.7	0.04	-3.0	-3.0

a) Torsion angle C(2)-*N*-(carbonyl-C)-(carbonyl-O).
b) Torsion angle C(6)-*N*-(carbonyl-C)-C_{ipso}.

Finally, although a safe determination of the existence of hydrogen bonds from X-ray diffraction data is difficult owing to the uncertain position of the hydrogen atoms, the structures corresponding to **17a** and **31b** do seem to satisfy the requirements which are characteristic of O-H···O *intra*molecular bonding;[42] i. e., (1) the observed O···H distance is less than 2.4Å, (2) the distance between oxygens is equal to 2.72 ± 0.04Å, (3) the difference r(O···O) - r(O···H) falls in the 0.7 to 1.0Å range, and (4) the (O-H···O) angle is greater than 120° (*Table 5*).

Table 5. *Structural Data Supporting the Existence of Hydrogen-Bonding in **17a** and **31b**.*

Structure	R (O··H)[a)]	R (O··O)	R(O··O)-R(O··H)	χ[b)]
17a	1.96	2.64	0.68	136.8
31b	1.96	2.75	0.79	149.7

a) Distances in Å.
b) Bond angle in O-H··· O=C.

Space groups, cell constants, number of reflections measured, and final *R* values for the X-ray analyses described in this section are collected in Table 6.

Table 6. *Crystal Data of All New Structures*

	17a	**17b**	**18a**	**18b**	**22**	**23**	**31a**	**31b**
Formula	$C_{24}H_{30}N_2O_3$	$C_{24}H_{30}N_2O_3$	$C_{21}H_{32}N_2O_3$	$C_{21}H_{32}N_2O_3$	$C_{19}H_{26}N_2O_3$	$C_{18}H_{24}N_2O_2$	$C_{19}H_{26}N_2O_3$	$C_{19}H_{26}N_2O_3$
M_r	394.5	394.5	360.5	360.5	330.4	300.4	330.4	330.4
T	293	293	293	293	293	293	293	293
Crystal system	orthorhombic	monoclinic	orthorhombic	orthorhombic	monoclinic	monoclinic	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1/c$	$P2_1/n$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	9.119 (2)	11.930 (2)	8.820 (2)	6.700 (2)	8.440 (2)	8.650 (2)	6.910 (2)	9.000 (2)
b [Å]	9.782 (2)	6.830 (2)	8.860 (2)	16.740 (3)	23.930 (5)	11.960 (2)	12.180 (2)	9.090 (2)
c [Å]	24.959 (5)	13.590 (3)	26.270 (5)	18.450 (4)	9.540 (2)	16.140 (3)	22.320 (4)	22.200 (4)
α [°]	90.00	90.00	90.00	90.00	90.00	90.00	90.00	90.00
β [°]	90.00	100.00 (3)	90.00	90.00	100.00 (3)	96.80 (3)	90.00	90.00
γ [°]	90.00	90.00	90.00	90.00	90.00	90.00	90.00	90.00
V [Å^3]	2226.4 (8)	1090.5 (4)	2052.9 (8)	2069.3 (8)	1897.5 (7)	1658.0 (6)	1878.5 (7)	1816.2 (7)
Z	4	2	4	4	4	4	4	4
D_x (g cm^{-3})	1.177	1.201	1.166	1.157	1.157	1.203	1.168	1.208
F [000]	848	424	784	784	712	648	712	712
Unique reflect.	1700	1576	1585	1587	2486	2166	1451	1393
of which $I > 4\sigma$	1266	935	1198	1141	1594	1639	787	1002
Final R	5.27	7.11	7.37	5.69	5.43	5.34	4.61	4.17

EXPERIMENTAL PART

Melting points were determined on a *Büchi-510* apparatus in open capillary tubes, and are uncorrected. Infrared spectra were recorded on a *Perkin-Elmer FT-IR 1600* spectrophotometer. ^{1}H- and ^{13}C-Nmr spectra were recorded in *Varian-Gemini-200* spectrometers, in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ values (ppm) and coupling constants J are given in Hz. Optical rotations $[\alpha]_D$ were measured at room temperature in a *Perkin-Elmer 241* polarimeter, in 1 dm cells; concentration c in g/100 ml. THF was initially distilled over KOH and then heated to reflux over K/benzophenone (under argon) until the blue color of the benzophenone ketyl persisted; at this point the THF was distilled and handled by means of syringes and cannulas. The *n*-BuLi employed (*ca.* 1.6 M in *n*-hexane) was titrated prior to its use.[44] tlc: *Merck-DC-F_{254}* plates; detection by uv light. Flash column chromatography:[45] *Fluka silica gel 60 40-63 μm*, and a pressure of 0 2-0.6 bar. Microanalyses were performed by the microanalytical laboratories at ETH-Zürich.

General Procedure for the Aldol Additions of Pyrimidinone (2S,6R)-3 (LDA as base).[31] In a dry two-necked round-bottom flask, provided with addition funnel, rubber septa and thermometer, was placed under argon diisopropylamine (1.13 eq) in 10 ml of THF, and cooled to -6°C before the slow addition of 1.13 eq. of *n*-BuLi (*ca.* 1.6 M in *n*-hexane). The resulting solution was stirred at -6°C for 15 min and then cooled down to -78°C before the dropwise addition of one eq. of pyrimidinone (**3**) in 15 ml of THF. Stirring was continued for 45 min at -78°C in order to secure the complete formation of enolate **3**-Li. The aldehyde (1.3 to 2.1 eq.) was then added dropwise *via* syringe, and the reaction mixture was stirred at -78°C until no further changes were detected by tlc. At this point the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, allowed to warm-up to ambient temperature, diluted with an additional amount of water (until a fluid solution was obtained), and extracted with three portions of Et_2O. The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in a rotary evaporator.

General Procedure for the Aldol Additions of Pyrimidinone (2S)-6 (LHMDS as base).[38] In a dry 20 ml Schlenk-type flask, provided with rubber septa and thermometer, was placed under argon 0.23 ml (1 1 mmol, 1.1 eq.) of HMDS in 3 ml of THF, and cooled to -6°C before the slow addition of 0.7 ml (1.1 mmol, 1.1 eq.) of *n*-BuLi (*ca.* 1.6 M in *n*-hexane). The resulting solution was stirred at -6°C for 15 min, and then cooled to -78°C before the dropwise addition of a solution containing 0.29 g (1 mmol) of pyrimidinone (**6**) in 4 ml of THF. Stirring was continued for 1 h at -78°C in order to secure the complete formation of dienolate **6**-Li. The appropriate aldehyde (1.3 to 2.0 eq) was then added dropwise, either at -78°C (acetone-dry ice bath) or at -105°C (cyclohexene-liquid nitrogen bath), and the reaction mixture was stirred at the same temperature until no further changes were detected by tlc. At this point the reaction was quenched by the addition of 2 ml of acetic acid in 10 ml of THF, allowed to warm-up to 0°C, treated with 10 ml of a saturated $NaHCO_3$ solution, and extracted with three portions of Et_2O. The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in a rotary evaporator.

General Procedure for Heterogeneous Catalytic Hydrogenolysis. In a 100 or 450 ml autoclave was placed the catalyst under argon, and a solution of the benzylic amine in ethyl acetate was added slowly *via* syringe. The autoclave was flushed three times with nitrogen (10 atm) and then filled with hydrogen at the appropriate pressure, and shaken at the desired temperature (thermoelement). At the end of the reaction (no more consumption of hydrogen), the autoclave was cooled in a water bath, opened, and flushed twice with nitrogen. The resulting suspension was filtered over celite, the catalyst rinsed with ethyl acetate, and the filtrate concentrated in a rotary evaporator

(3R,1'R)-3-[(N-Benzyl-1'-phenylethyl)amino]-butanoic Acid Methyl Ester [(*R,R*)-**10**]. According to the general procedure of *Davies* and *Ichihara*,[13e] 1.1 g (5.2 mmol) of (*N*-benzyl-1'-phenylethyl)amine (**9**)[27] in 30 ml of dry THF was placed under argon in a dry 100 ml two-necked round-bottom flask, and cooled to 0°C before the dropwise addition of 3.3 ml (5.2 mmol) of *n*-BuLi (*ca.* 1.6 M in *n*-hexane). The resulting wine-red solution was stirred for 15 min at 0°C and then cooled to -78°C before the dropwise addition of 0.29 g (2.9 mmol) of (*E*)-crotonic acid methyl ester in 20 ml of dry THF. Stirring was continued for 15 min at -78°C, the reaction mixture was quenched with 10 ml of saturated NH_4Cl aqueous solution (orange → yellow), allowed to warm-up to ambient temperature, and then extracted with three 30 ml portions of Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in a rotary evaporator to afford the crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 4:1) to give 0.80 g (90% yield) of ester (**10**) as a pale yellow oil with R_f = 0.46 (*n*-hexane/ethyl acetate, 4:1). bp 180-190°C/0.2 Torr. ^{1}H-Nmr: 1 15 (d, J = 6.0, CH_3-C(3)); 1.36 (d, J = 7.5, CH_3-C(1')); 2.13 (dd, J_1 = 12.0, J_2 = 7.5, H-C(2)); 2.40 (dd, J_1 = 12.0, J_2 = 5.0, H-C(2)); 3.46 (m, H-C(3)); 3.52 (s, OCH_3); 3.73 (s, NCH_2-Ph); 3.90 (q, J = 7.5, H-C(1')); 7.15-7.49 (m, 10 arom. H).

(R)-3-Aminobutanoic Acid Methyl Ester [(*R*)-**11**]. According to the general procedure described above for hydrogenolysis, 1.0 g (3.2 mmol) of benzylic amine (**10**) was dissolved in 10 ml of ethyl acetate and treated with 0.15 g of $Pd(OH)_2$/C and 30 atm of H_2 at 50°C during 25 h. The described workup procedure afforded 0.31 g (2.6 mmol, 81% yield) of β-amino ester (**11**), bp 50-60°C/ 0.1 Torr. $[\alpha]_D$ = -29.0° (c = 0 45, $CHCl_3$). ^{1}H-Nmr: 1.11 (d, J = 6.0, CH_3-C(3)); 1.51 (br s, NH); 2.29, 2.42 (AB, J = 15, J' = 9.5, J'' = 5.5, CH_2); 3.38 (m, H-C(3)); 3.69 (s, OCH_3).

(3R,1'S)- and (3S,1'S)-3-[(1'-Phenylethyl)amino]butanoic Acid Methyl Esters [(*R,S*)- and (*S,S*)-**12**]. According to the literature procedure,[23b,24a] a solution of 22.8 ml (216 mmol) of (*E*)-crotonic acid methyl ester and 30.3 g (250 mmol) of (*R*)-1-phenylethylamine in 86 ml of methanol was heated to reflux for 4 d. Following concentration in a rotary evaporator, the crude product (yellow oil) was distilled in a Kugelrohr apparatus [100-103°C/0.4 Torr; lit.,[23b] bp 90-96°C/0.2 Torr] to afford 36.9 g (167 mmol, 67% yield) of a colorless fluid oil which according to ^{1}H-Nmr contained two diastereoisomeric products in a 3:2 ratio. Separation of the mixture was accomplished by gradient flash chromatography (*n*-hexane/ethyl acetate, 4:1 → 7:3) yielded pure fractions of (*R,S*)-**12** (18.0 g, 81.4 mmol, 33% yield) and (*S,S*)-**12** (14.7 g, 66.5 mmol, 27% yield).

(3*R*,1'*S*)-**12**: R_f = 0.29 (*n*-hexane/ethyl acetate, 3:1) bp 110-120°C/0.2 Torr. $[\alpha]_D$ = -35.8° (c = 0.50, $CHCl_3$). lit.,[24a] $[\alpha]_D$ = -39.1° (c = 0.97, $CHCl_3$) ^{1}H-Nmr: 1.07 (d, J = 6.0, CH_3-C(3)); 1.33 (d, J = 6.0, CH_3-C(1')); 1.63 (s, NH); 2.20-2.43 (m, CH_2); 2.88 (m, J = 6.0, H-C(3)); 3 62 (s, OCH_3); 3.90 (q, J = 6.0, H-C(1')); 7.16-7.38 (m, 5 arom H).

(3*S*,1'*S*)-**12**: R_f = 0.19 (*n*-hexane/ethyl acetate, 3:1) bp 120°C/0.1 Torr. $[\alpha]_D$ = -46.3° (c = 1.15, $CHCl_3$). lit.,[24a] $[\alpha]_D$ = -49 6° (c = 1.25, $CHCl_3$). ^{1}H-Nmr: 1 04 (d, J = 6.0, CH_3-C(3)); 1.31 (d, J = 6.0, CH_3-C(1')); 1.49 (br s, NH); 2.28-2.51 (m, CH_2); 2 97 (m, H-C(3)); 3.66 (s, OCH_3); 3.87 (q, J = 6.0, H-C(1')); 7.15-7.36 (m, 5 arom. H).

(R)-3-Aminobutanoic Acid methyl Ester [(*R*)-**11**] *by hydrogenolysis of (R,S)-12*. According to the general procedure described above, 10.0 g (45.2 mmol) of the secondary benzylic amine ((*R,S*)-**12**) was dissolved in 105 ml of ethyl acetate, and hydrogenolyzed with H_2 (30 atm) and 1.0 g of Pd/C catalyst at 50°C. Concentration of the reaction mixture (rotary evaporator) gave 6.0 g of the crude product containing the desired product and some ethylbenzene. From integration of the ^{1}H-Nmr spectrum, a yield greater than 90% was estimated for (*R*)-**11** which was used directly in the next step (**11** → **13**). For the physical and spectroscopic properties of (*R*)-**11** see above.

(R)-3-Aminomethylbutanamide [(*R*)-**13**]. According to the procedure in the literature,[24a] 11.9 g (101 mmol) of (*R*)-**11** in 140 ml of methanol were cooled to 0°C and treated dropwise with 51.8 ml (614 mmol) of methylamine (40% in H_2O, 11.85 M). The resulting solution was stirred at 0°C during 4 d and then concentrated in the rotary evaporator to give 16.1 g (*ca.* 100% yield) of crude product [*^{1}H-Nmr: 1.12 (d, J = 6.0, CH_3-C(3)); 1.65 (br s, NH, NH_2); 2.09 (dd, J_1 = 15.0, J_2 = 9.5, H_A-C(2)); 2.30 (dd, J_1 = 15.0, J_2 = 5.5, H_B-C(2)); 2.78 (d, J = 5.0, CH_3-NH); 3.23 - 3.40 (m, H-C(3))*], which was used without further manipulation in the following transformation (**13** → **14**).

(R)-3-[(2',2'-Dimethylpropyliden)amino]-N-*methylbutanamide* [(*R*)-**14**]. According to the described procedure,[24a] 16.1 g (*ca.* 101 mmol) of the crude product (*R*)-**13** was dissolved in 112 ml of CH_2Cl_2, treated with 28.4 ml (204 mmol) of triethylamine, and then dropwise with 22.3 ml (203 mmol) of pivalaldehyde. The reaction mixture was heated to reflux for 7 h with concomitant removal of water, until 2.2 ml of it had been collected. Concentration in the rotary evaporator afforded 17.2 g (*ca.* 100% yield) of the desired imine, which was immediately used for the formation of pyrimidinone **3** ^{1}H-Nmr: 1.03 (s, *t*-Bu); 1.16 (d, J = 6 0, CH_3-C(3)); 2.30 (dd, J_1 = 20, J_2 = 7.5, H_A-C(2)); 2.40 (dd, J_1 = 20, J_2 = 4.0, H_B-C(2)), 2.75 (d, J = 5.0, CH_3-NH); 3.50 (m, H-C(3)); 6.73 (br s, NH); 7.51 (s, H-C(1')).

1-Benzoyl-2(S)-tert-*butyl-3,6(R)- and 1-Benzoyl-2(R)*-tert-*butyl-3,6(R)-dimethylperhydropyrimidin-4-one* [(2*S*,6*R*)-**3** and (2*R*,6*R*)-**15**] Following the procedure reported previously,[24a] 16.1 g (*ca.* 101 mmol) of imine (*R*)-**14** was dissolved in 600 ml of toluene, treated with 11.15 g (91.3 mmol) of DMAP, and then dropwise with 16 8 ml (145 mmol) of benzoyl chloride. The reaction mixture was heated to reflux for 24 h and the precipitate that formed was filtered and rinsed with 60 ml of toluene. The filtrate was concentrated in a rotary evaporator to give 31 g of the red-brown crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:1 → 1·4) to give 8.60 g (29.9 mmol, 29.6% yield) of (2*S*,6*R*)-**3**, and 1.44 g (5.0 mmol, 5% yield) of (2*R*,6*R*)-**15**.

(2*S*,6*R*)-**3**. Recrystallized from *n*-hexane/ethylacetate, *ca.* 19:1. R_f = 0.25 (*n*-hexane/ethyl acetate, 1:2). mp 106-107°C $[\alpha]_D$ = -89° (c = 0 57, $CHCl_3$) [lit.,[24a] mp 104-105°C. $[\alpha]_D$ = -94.6 (c = 1.3, $CHCl_3$)]. ^{1}H-Nmr: 1.05 (s, *t*-Bu); 1.26 (br d, CH_3-C(6)); 2.65 (d, J = 10.0, CH_2); 3.10 (s, NCH_3); 4.38 (br m, H-C(6)); 5.53 (br s, H-C(2)); 7 24-7.47 (m, 5 arom. H).

(2*R*,6*R*)-**15**. Recrystallized from *n*-hexane/ethylacetate, *ca* 19:1. R_f = 0 18 (*n*-hexane/ethyl acetate, 1 2). [lit.,[24a] mp 169-170°C. $[\alpha]_D$[24a] = +124° (c = 0.8, $CHCl_3$). ^{1}H-Nmr: 1.00 (d, J = 6.0, CH_3-C(6)); 1.08 (s, *t*-Bu); 2.24, 2.35 (AB, J = 22 5, J' = 2.5, CH_2); 3.17 (s, NCH_3); 4.42 (m, H-C(6)); 6.18 (br s, H-C(2)); 7.35-7.80 (5 arom. H).

1-Benzoyl-2(S)-tert-*butyl-3,6(R)-dimethyl-5(S)-[1'(R)-] and [1'(S)-hydroxybenzyl]tetrahydropyrimidin-4-one* (**17a** and **17b**). According to the general procedure for aldol (enolate) reactions described above, 0.86 g (3.0 mmol) of pyrimidinone ((2*S*,6*R*)-**3**), 0.48 ml (3.4 mmol) of diisopropylamine (DIPA), 2.1 ml of *n*-BuLi (3.4 mmol, *ca.* 1.6 M), and 0.49 ml (4.8 mmol, 1.6 eq) of benzaldehyde were allowed to react (reaction time = 6 h). The described workup procedure (10 ml of saturated NH_4Cl, 5 ml of H_2O, two 20 ml portions of Et_2O) afforded 1.62 g of a yellowish, crude product. Flash chromatography (*n-hexane/ethyl acetate, 1:1*) gave 0.67 g (1.7 mmol, 57% yield) of diastereoisomer (**17a**) and 0.31 g (0.8 mmol, 26% yield) of diastereoisomer (**17b**).

(1'*R*)-**17a**. R_f = 0.49 (*n*-hexane/ethyl acetate, 1:2). mp 143-145°C. $[\alpha]_D$ = -86.7° (c = 0.29, $CHCl_3$). Ir ($CHCl_3$): 3440br, 3010m, 2965m, 1630s, 1485m, 1415s, 1395s, 1350s, 1160w, 1105w, 1025w, 600w. ^{1}H-Nmr: 0.88 (br d, $w_{1/2} \approx 18$, CH_3-C(6)); 1.06 (s, *t*-Bu); 2.89 (br m, $w_{1/2} \approx 20$, 1H); 3.11 (s, NCH_3); 4.25 (br s, $w_{1/2} \approx 35$, 1 H); 4.79 (br m, $w_{1/2} \approx 15$, 1 H); 5.52 (br s, $w_{1/2} \approx 13$, 1 H); 7.15-7.46 (m, 10 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 1.03 (s, *t*-Bu); 1.18 (d, J = 6.6, CH_3-C(6)); 2.95 (dd, J_1 = 12.0, J_2 = 3.4-4.0, H-C(5)); 3.01 (s, NCH_3); 4.10 (m, H-C(6)); 5.32 (br s, H-C(1')); 5.45 (2 s, H-C(2), OH); 6.92 (d, J = 6.8, 2 arom. ortho-H); 7.20-7.40 (m, 8 arom. H). ^{13}C-Nmr: 22.0 (2 br), 27.8, 38.0, 38.8, 49.7, 51.0, 74.0, 125.8, 126.3, 127.5, 128.1, 128.4, 129.1, 136.1, 141.2, 171.2, 171.6. Ms: 394 (M^+, <1), 379 (<1), 361 (<1), 337 (32), 231 (56), 215 (4), 131 (7), 105 (100), 77 (58), 51 (12), 42 (12), 28 (17). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C 73.07, H 7.66, N 7.10; found: C 73.36, H 7.67, N 7.07.

(1'*S*)-**17b**. R_f = 0.29 (*n*-hexane/ethyl acetate, 1:2). mp 119-120°C. $[\alpha]_D$ = -185.7° (c = 0.23, $CHCl_3$). Ir ($CHCl_3$): 3425br, 3005m, 1625s, 1490w, 1415m, 1400m, 1355m, 1160w, 1105w, 1045w, 1000w, 920w, 600w. ^{1}H-Nmr: 0.71 (br, $w_{1/2} \approx 25$, CH_3-C(6)); 1.10 (br s, $w_{1/2} \approx 10$, *t*-Bu); 2.90 (br $w_{1/2} \approx 16$, 1 H); 3.20 (s, NCH_3); 4.05 - 4.50 (br, 1H + OH, D_2O-exchange); 5.44 (br, $w_{1/2} \approx 15$, 1 H); 5.92 (br, $w_{1/2} \approx 23$, 1 H); 7.10-7.41 (m, 10 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 0.61 (d, J = 6.6, CH_3-C(6)); 1.01 (s, *t*-Bu); 2.64 (dd, J_1 = 6.2, J_2 = 0.7, H-C(5)); 3.06 (s, NCH_3); 4.50 (m, H-C(6)); 5.17 (s, OH); 5.56, 5.62 (2 s, H-C(1'), H-C(2)); 7.09-7.49 (m, 10 arom. H). ^{13}C-Nmr: 22.7 (2 br), 38.5, 38.6, 47.8, 51.0, 71 9, 125.8, 126.0, 127.2, 128.2, 128.3, 128.9, 136.1, 140.3, 170.5. Ms: 394 (M^+, <1); 379 (<1), 361 (<1), 337 (7), 319 (2), 231 (54), 105 (100), 77 (46), 51 (13), 42 (9), 28 (12). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C 73.07, H 7.66, N 7.10; found: C 73.26, H 7.65, N 7.06.

1-Benzoyl-2(S)-tert-butyl-3,6(R)-dimethyl-5(S)-[1'(S)-] and [1'(R)-hydroxyisobutyl]tetrahydropyrimidin-4-one (**18a** and **18b**). According to the general procedure for aldol (enolate) reactions described above, 0.75 g (2.5 mmol) of pyrimidinone ((2*S*,6*R*)-**3**), 0.40 ml (2.8 mmol) of DIPA, 1.89 ml of *n*-BuLi (2.8 mmol), and 0.29 ml (3 2 mmol, 1.3 eq.) of isobutyraldehyde were allowed to react (reaction time = 3 h). The described workup procedure (10 ml of saturated aqueous NH_4Cl, 5 ml of H_2O, three 20 ml portions of Et_2O) afforded 0.93 g of the crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:2) to give 0.46 g (1.3 mmol, 51% yield) of diastereoisomer (**18a**) and 0.12 g (0.3 mmol, 13% yield) of diastereoisomer (**18b**).

(1'*S*)-**18a**: R_f = 0.48 (*n*-hexane/ethyl acetate, 1:2). mp 115-117°C. $[\alpha]_D$ = -54.3° (c = 0.27, $CHCl_3$). Ir ($CHCl_3$): 3485br, 3005m, 2965m, 2875w, 1630s, 1485w, 1395m, 1355s, 1120w, 1070w, 1005w, 845w, 650w, 615w. ^{1}H-Nmr: 0.84 (d, J = 7.0, CH_3-^{i}Pr), 1.04 (d, J = 7.0, CH_3-^{i}Pr); 1 09 (s, *t*-Bu); 1.27 (br, CH_3-C(6)); 2.30 (m, H-C(2')); 2.85 (d, J = 10.0, H-C(5)); 2.85 (br, 1 H); 3.11 (s, NCH_3); 3.52 (d, J = 12.5, OH, D_2O-Exchange); 4.40 (br s, $w_{1/2} \approx 28$, 1H); 5.79 (br s, $w_{1/2} \approx 55$, 1 H); 7.25-7.45 (m, 5 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 0.78 (d, J = 6.8, CH_3-^{i}Pr); 0.93 (d, J = 6.6, CH_3-^{i}Pr), 1.01 (s, *t*-Bu); 1.32 (d, 6.3, CH_3-C(6)); 2.16 (m, H-C(2'); 2.68 (dd, J_1 = 9.7, J_2 = 1.1, H-C(5)); 3.02 (s, NCH_3); 3.16 (ddd, J_1 = 8.5, J_2 = 8.5, J_3 = 1.5, H-C(1')); 4 03 (d, J = 1 3, OH); 4.34 (m, H-C(6)); 5.41 (s, H-C(2)); 7.25-7.34 (m, 2 arom. H); 7.41-7 49 (m, 3 arom. H). ^{13}C-Nmr: 20.2, 20.2, 28.5, 33.1, 38.1, 39.4, 46.3, 51.4, 77.6, 126.6, 129.0, 129.6, 137.0, 171.7, 171.9. Ms: 361 ($(M+1)^+$, <1), 345 (<1), 317 (3), 303 (73), 231 (8), 181 (13), 105 (100), 85 (9), 77 (27), 57 (5), 41 (14), 18 (5). Anal. Calcd for $C_{21}H_{32}N_2O_3$: C 69.97, H 8.95, N 7.77; found. C 70.07, H 8.79, N 7.69.

(1'*R*)-**18b**: R_f = 0.30 (*n*-hexane/ethyl acetate, 1:2). mp 136-137°C. $[\alpha]_D$ = -54.1° (c = 0.32, $CHCl_3$). Ir ($CHCl_3$): 3450br, 3005m, 2965m, 2875w, 1630s, 1485m, 1460m, 1415m, 1395m, 1350s, 1155w, 1115m, 995w, 660w, 640w. ^{1}H-Nmr: 0.85 (d, J = 7.0, CH_3-^{i}Pr); 0.99 (d, J = 7.0, CH_3-^{i}Pr); 1.10 (s, *t*-Bu); 1.40 (br s, CH_3-C(6), H-C(2')); 2.78 (br d, $w_{1/2} \approx 18$, H-C(5)); 2.90 (br s, $w_{1/2} \approx$ 15, OH, D_2O-exchange); 3.12 (s, NCH_3); 3.98 (dq, J_1 = 10.0, J_2 =2.5, H-C(6)); 4.57 (br s, $w_{1/2} \approx 30$, H-C(1')); 5.92 (br s, $w_{1/2} \approx 55$, H-C(2)); 7.28-7.46 (m, 5 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 0.79 (d, J = 6.7, CH_3-^{i}Pr); 0.87 (d, J = 6.5, CH_3-^{i}Pr); 1.04 (s, *t*-Bu); 1.34 (d, J = 6.6, CH_3-C(6)); 1.52 (m, H-C(2')); 2.47 (br s, H-C(5)); 2.99 (s, NCH_3), 3.95 (br m, $w_{1/2} \approx 10$, H-C(1')); 4.43 (br s, $w_{1/2} \approx 8$, OH); 4.54 (m, J = 5.2, H-C(6)); 5.49 (br s, $w_{1/2} \approx 10$, H-C(2)); 7.29-7.47 (m, 5 arom. H). ^{13}C-Nmr: 19.9, 19.9, 23.4 (br), 28.3, 30.6, 38.7, 39.4, 47.9, 76.4, 126.6, 128.9, 129.7, 137 0, 171.6, 171.8 Ms: 361 ($(M+1)^+$, <1), 345 (<1), 317 (1), 303 (48), 231 (9), 181 (6), 105 (100), 85 (6), 77 (25), 57 (4), 41 (8), 28 (18), 18 (9). Anal. Calcd for $C_{21}H_{32}N_2O_3$: C 69.97, H 8.95, N 7.77; found: C 70 23, H 8.88, N 7 71.

1-Benzoyl-2(S)-tert-butyl-3,6(R)-dimethyl-5(S)-[1'(S)-] and [1'(R)-hydroxyethyl]tetrahydropyrimidin-4-one (**19a** and **19b**). According to the general procedure of aldol (enolate) reactions described above, 0.75 g (2.5 mmol) of pyrimidinone ((2*S*,6*R*)-**3**), 0.40 ml (2.8 mmol) of DIPA, 1.8 ml (2.8 mmol) of *ca.* 1.6 M *n*-BuLi, and 0.30 ml (5.3 mmol, *ca.* 2.1 eq.) of acetaldehyde were allowed to react (reaction time = 3 h). The described workup procedure (10 ml of saturated aqueous NH_4Cl, 5 ml of H_2O, three 20 ml portions of Et_2O) afforded 0.96 g of the crude product, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 2:1) to give 0.48 g (1.4 mmol, 58% yield) of diastereoisomer (**19a**) and 0.13 g (0.4 mmol, 16% yield) of diastereoisomer (**19b**).

(1'*S*)-**19a**: R_f = 0.21 (*n*-hexane/ethyl acetate, 1:2). mp 116-117°C. $[\alpha]_D$ = -33.9° (c = 0.35, $CHCl_3$). Ir ($CHCl_3$): 3465br, 3005m, 1630s, 1485w, 1460m, 1410s, 1395s, 1350s, 1125m, 1100m, 1015w, 645w. ^{1}H-Nmr: 1.07 (s, *t*-Bu); 1.26 (d, J = 6.2, CH_3); 1.40 (br s, $w_{1/2} \approx 25$, CH_3); 2.81 (br d, $w_{1/2} \approx 18$, H-C(5)); 3.11 (s, NCH_3); 3.95 (br m, $w_{1/2} \approx 23$, 1 H); 4.11 (br s, $w_{1/2} \approx 25$, 1 H); 4.32 (d, J = 10.0, OH, D_2O-exchange); 5.57 (br s, $w_{1/2} \approx 60$, H-C(2)); 7.25 - 7.48 (m, 5 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 1.02 (s, *t*-Bu); 1.07 (d, J = 6.2, CH_3-C(1')); 1.36 (d, J = 6.6, CH_3-C(6)); 2.37 (dd, J_1 = 4.7, J_2 = 1.1-1.4, H-C(5)); 2.99 (s, NCH_3);

4.25-4.46 (m, H-C(6), H-C(1'), OH); 5.46 (s, H-C(2)); 7.32 (s, 2 arom. H); 7.42 (s, 3 arom. H). ^{13}C-Nmr: 18.8, 28.3, 38.0, 39.6, 49.7, 50.1, 67.7, 77.5, 126.4, 129.1, 129.8, 136.7, 171.5, 171.9. Ms. 333 ((M+1)$^+$, <1), 317 (<1), 275 (20), 257 (7), 231 (15), 153 (6), 105 (100), 77 (21), 41 (5) Anal. Calcd for $C_{19}H_{28}N_2O_3$: C 68.65, H 8.49, N 8.43; found: C 68.83, H 8.65, N 8.39.

(1'*R*)-**19b**: R_f = 0.29 (*n*-hexane/ethyl acetate, 1:2). mp 88-89°C. $[\alpha]_D$ = -32.1° (c = 0 43, $CHCl_3$). Ir ($CHCl_3$): 3480br, 3005s, 2870s, 1630s, 1485m 1460m, 1415s, 1395s, 1350s, 1125m, 1040m, 925w, 850w, 645w. ^{1}H-Nmr: 1.07 (s, *t*-Bu); 1.42 (d, J = 6.6, CH_3); 1.0 - 1.5 (br, CH_3); 2.51 (dd, J_1 = 10, J_2 = 2.8, H-C(5)); 3.11 (s, NCH_3); 3.64 - 4.47 (m, H-C(6), OH, H-C(1')); 5.59 (br s, $w_{1/2} \approx 90$, H-C(2)); 7.25-7.47 (m, 5 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 80°C): 1.02 (s, *t*-Bu); 1.07 (d, J = 6.2, CH_3-C(1')); 1.38 (d, J = 6.0, CH_3-C(6)); 2 60 (dd, J_1 = 7.6, J_2 = 2.4-3.3, H-C(5)); 2.96 (s, NCH_3); 4.2-4.4 (m, H-C(6), H-C(1')); 4.40 (d, J = 4.0, OH); 5.44 (br s, H-C(2)); 7.28-7.33 (m, 2 arom. H); 7.42-7.49 (m, 3 arom. H). ^{13}C-Nmr: 22.4, 23.1, 28.4, 38.3, 39.5, 50.8, 67.9, 77.5, 126.6, 129.0, 129.7, 136.9, 171.9 (2×). Ms 333 ((M+1)$^+$, <1), 317 (<1), 275 (44), 257 (4), 231 (19), 153 (13), 105 (100), 77 (20), 42 (4), 28 (24), 18 (7). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C 68.65, H 8.49, N 8.43; found: C 68.80, H 8.37, N 8.08.

*1-Benzoyl-2(*S*)-*tert*-butyl-3,6-dimethyl-5-bromodihydropyrimidin-4-one* (**20**) *and 1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5-bromo-6-(bromomethyl)dihydropyrimidin-4-one* (**21**). Following the procedures described in the literature,[36a,46] 4.7 g (16.3 mmol) of pyrimidinone ((2*S*,6*R*)-**3**) in 80 ml of CCl_4 was treated with 6.1 g (34.3 mmol) of *N*-bromosuccinimide and 0.06 g (catalytic amount) of 2,2'-azobisisobutyronitrile (AIBN, radical initiator), and heated to reflux under argon for 7 h. The reaction mixture was then cooled to 0°C, filtered, and concentrated in a rotary evaporator to afford 5.3 g of the crude product, which was used without further purification in the next step (debromination to (2*S*)-**6**). Analysis of the ^{1}H-Nmr spectrum of this material indicates a 2:1 mixture of monobromide (**20**) and dibromide (**21**).

(2*S*)-**20**: R_f = 0.24 (*n*-hexane/ethyl acetate, 2:1). ^{1}H-Nmr. 1.03 (s, *t*-Bu); 1.70 (s, CH_3-C(6)); 3.24 (s, NCH_3); 5.60 (s, H-C(2)); 7 40 - 7.58 (m, 5 arom. H).

(2*S*)-**21**: R_f = 0.16 (*n*-hexane/ethyl acetate, 2:1) ^{1}H-Nmr: 1.12 (s, *t*-Bu), 3.22 (s, NCH_3), 3.52 (d, J = 12 5, H-C(1')), 4.28 (d, J = 12.5, H-C(1')), 5.51 (s, H-C(2)), 7.40-7.58 (m, 5 arom. H).

*(2S)-1-Benzoyl-2-*tert*-butyl-3,6-dimethyldihydropyrimidin-4-one* [(2*S*)-**6**]. According to the literature procedures,[36a,46] 5.3 g (*ca.* 16 7 mmol) of the mixture of bromides (**20**) and (**21**) was dissolved in 150 ml of ethanol and treated with 4.77 ml (34.2 mmol) of triethylamine and 1.05 g of Pd/C under 10 atm of H_2 and at 45°C during 6.5 h. The described hydrogenolysis workup procedure (see above) gave after flash chromatography (*n*-hexane/ethyl acetate, 1:3) 2.3 g (8 mmol, 55-60% yield) (2*S*)-**6** and 0.40 g (1.2 mmol, *ca.* 10% yield) *rac*-**22**.

(2*S*)-**6**: R_f = 0.32 (*n*-hexane/ethyl acetate, 1:3). mp 116-117°C. $[\alpha]_D$ = +442.7° (c = 1.01, $CHCl_3$). Ir ($CHCl_3$): 3010m, 2980m, 1675m, 1645s, 1480w, 1400m, 1335s, 1280m, 1140m, 1085w, 1045w, 880w, 840m, 620w. ^{1}H-Nmr: 1.05 (s, *t*-Bu); 1.57 (s, CH_3-C(6)); 3.17 (s, NCH_3); 5.48 (s, H-C(2)); 5.59 (s, H-C(5)); 7 38 - 7.58 (m, 5 arom. H). ^{13}C-Nmr: 22.5, 27 7, 37.0, 40.4, 79.3, 113.2, 128.2, 129.1, 131.9, 136.3, 146.9, 163.4, 170.1. Ms: 271 ((M-15)$^+$, <1), 229 (28), 105 (100), 77 (19), 51 (2), 42 (5), 28 (27), 18 (18) Anal. Calcd for $C_{17}H_{22}N_2O_2$: C 71 30, H 7.74, N 9.78; found· C 71.35, H 7.63, N 9.59.

rac-*1-Benzoyl-2-*tert*-butyl-3-(ethoxymethyl)-6-methyldihydropyrimidin-4-one* [(*rac*)-**22**]. R_f = 0.53 (*n*-hexane/ethyl acetate, 1:3) *mp* 136-137°C. $[\alpha]_D$ = +5.8° (c = 0.38, $CHCl_3$). Ir ($CHCl_3$): 3005m, 2975m, 2870w, 1675s, 1650s, 1450m, 1390m, 1330s, 1260m, 1160w, 1130m, 1055m, 840m, 625m. ^{1}H-Nmr: 1.04 (s, *t*-Bu); 1.10 (t, J = 6.9, OCH_2CH_3); 1.59 (s, CH_3-C(6)); 3.47 (m, OCH_2CH_3); 4.42 (d, J = 10.5, NCH_2O); 5.48 (s, H-C(2)); 5.58 (d, J = 10.6, NCH_2O); 5.83 (s, H-C(5)); 7.35-7.55 (m, 5 arom. H). ^{13}C-Nmr: 15.1, 22.7, 27.5, 40.0, 64.1, 74.6, 75.8, 112.5, 128.1, 129.2, 131.9, 136.4, 148.4, 164.2, 169.8. Ms: 285 ((M-45)$^+$, 2), 273 (29), 152 (3), 105 (100), 77 (15), 51 (2), 41 (2), 32 (5), 28 (23), 18 (5). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C 69.06, H 7.93, N 8.48; found: C 68.82, H 8.14, N 8.28.

*(2S,5R)-1-Benzoyl-2-*tert*-butyl-3,5-dimethyl-6-methylenedihydropyrimidin-4-one* [(2*S*,5*R*)-**23**]. Following the general procedure described above for the alkylation of dienolate (**6**), 0.57 g (2 mmol) of pyrimidinone (**6**) was dissolved in 14 ml of THF and metallated with 1.1 eq. of LDA (0.32 ml of DIPA and 1.4 ml *n*-BuLi, *ca.* 1.6 M), and treated with 0.16 ml (2.6 mmol, 1.3 eq.) of methyl iodide (reaction time = 4 h). The usual workup procedure afforded after flash chromatography (*n*-hexane/ethyl acetate, 1:2) 0.22 g (0.73 mmol, 37% yield) of **23**. R_f = 0.43 (*n*-hexane/ethyl acetate, 1:2). mp 110-112°C. $[\alpha]_D$ = +124.1° (c = 0.27, $CHCl_3$). Ir ($CHCl_3$): 3005m, 2975m, 2870w, 1650s, 1635s, 1485m, 1445s, 1410s, 1395s, 1370m, 1340s, 1320s, 1150m, 1110w, 890w, 650w. ^{1}H-Nmr: 1.10 (s,*t*-Bu); 1.60 (d, J = 7.5, CH_3-C(5)); 3.16 (s, NCH_3), 3.25 (q, J = 7.5, H-C(5)); 4.40 (s, H-C(1')); 4.79 (s, H-C(1')); 5.70 (s, H-C(2)); 7.29-7 45 (m, 5 arom. H). ^{13}C-Nmr: 21.4, 27 2, 38.4, 40.7, 41.2, 75.6, 111.8, 128.0, 128.4, 130.3, 135.8, 144.8, 169.8, 171.6. Ms: 300 (M$^+$, <1), 285 (<1), 257 (2), 243 (48), 138 (3), 105 (100), 77 (21), 42 (6), 18 (11). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C 71.97, H 8.05, N 9.33; found: C 72.20, H 8.26, N 9.13.

*(2S,5R)-1-Benzoyl-2-*tert*-butyl-3-methyl-6-methylenedihydropyrimidin-4-one* [(2*S*)-**24**]. Obtained as side product (35% yield) in the previous alkylation reaction. R_f = 0.33 (*n*-hexane/ethyl acetate, 1:3). ^{1}H-Nmr: 1.10 (s, *t*-Bu); 3.18 (s, NCH_3), 3.29 (d, J = 20.5, C(5)H_A); 3.56 (dt, J_1 = 20.5, J_2 = 3.0, C(5)H_B); 4.36 (s, H-olef.); 4.69 (s, H-olef.); 5 64 (s, H-C(2)); 7.31-7.45 (m, 5 arom. H).

*1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-[1'(*S*)-hydroxybenzyl]-6-methylenedihydropyrimidin-4-one* [(2*S*,5*S*,1'*S*)-**30**]. Following the general procedure described above for aldol (dienolate) reactions, with 0.20 ml (2 mmol, 2 eq.) of benzaldehyde, at -78°C, and with a reaction time of 1.5 h. The described workup procedure gave 0.58 g of the crude product (yellow solid), which was purified by flash chromatography to give 0.32 g (0.82 mmol, 82% yield) of pure **30**. R_f = 0.43 (*n*-hexane/ethyl acetate, 1:2). mp 156-158°C. $[\alpha]_D$ = +79.0° (c = 0.41, $CHCl_3$). Ir ($CHCl_3$): 3010m, 2975m, 1670m, 1635s, 1485m, 1455m, 1405s, 1325s, 1050m, 890w, 625w. ^{1}H-Nmr. 0.92 (s, *t*-Bu); 2.99 (br s, $w_{1/2} \approx$ 12.5, NCH_3); 3 67 (br s, $w_{1/2} \approx$ 10, 1H); 5.38 (br s, $w_{1/2} \approx$ 20, 1H); 6.89 (br s, $w_{1/2} \approx$ 35, 1H); 3.8-6.4 (br, 3H); 7.10-7.45 (m, 10 arom. H). ^{13}C-Nmr: 27.1, 37.8, 41.5, 53.2, 77.1, 77.5, 114.2, 127.0, 127.6, 128.1, 128.5, 128.6, 130 6, 135.6, 137.9, 141.3, 169.7, 170.8. Ms: 335 ((M-57)$^+$, <1), 317 (<1), 286 (<1), 271 (<1), 229 (36), 105 (100), 77 (33), 43 (11), 28 (6), 18 (19). Anal. Calcd for $C_{24}H_{28}N_2O_3$: C 73.44, H 7.19, N 7.14; found: C 73.20, H 7.42, N 6.92.

*1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-[1'(*R*)-] and [1'(*S*)-hydroxyethyl]-6-methylenedihydropyrimidin-4-one* [1'(*R*)-**31a** and 1'(*S*)-**31b**]. Following the general procedure described above for aldol (dienolate) reactions, with 0.07 ml (1.3 mmol, 1.3 eq.) of acetaldehyde, at -78°C, and with a reaction time of 2.5 h. The usual workup procedure gave 0.35 g of the crude product (yellow solid), which was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:2) to give 0.17 g (0.51 mmol, 51% yield) of diastereoisomer (**31a**) and 80 mg (24% yield) of diastereoisomer (**31b**).

(1'*R*)-**31a**: R_f = 0.23 (*n*-hexane/ethyl acetate, 1:2). mp 171-173°C. $[\alpha]_D$ = +184.2° (c = 0.65, $CHCl_3$). Ir ($CHCl_3$). 3430br, 3010m, 2975m, 1625s, 1485m, 1405s, 1330s, 1075m, 1045w, 890m, 650w. ^{1}H-Nmr: 1.01 (s, *t*-Bu); 1.22 (d, J = 6.3, CH_3-C(1')); 3 10 (s, NCH_3), 3.31 (br d, $w_{1/2} \approx$ 6.5, H-C(5)); 4.12 (br d, $w_{1/2} \approx$ 14, OH); 4.28 (br m, $w_{1/2} \approx$ 15, H-C(1')); 5.00 - 5.16 (2 br s, H-C(2), H-olef.); 5.33 (br s, $w_{1/2} \approx$ 10, H-olef.); 7.32-7.50 (m, 5 arom. H). ^{1}H-Nmr (300 MHz, DMSO-d_6, 100°C): 1.11 (d, J = 6.4, CH_3-C(1')); 2.93 (d, J = 2.0, H-C(5)); 3.04 (s, NCH_3); 4.46 (m, H-C(1')), 4.66 (s, H-olef.); 4.70 (s, OH); 4.86 (s, H-olef.), 5.54 (s, H-C(2)); 7.31-7.48 (m, 3 arom. H); 7.63-7 70 (m, 2 arom. H). ^{13}C-Nmr: 19.5, 26 7, 37.3, 40.5, 52.1, 72.4, 77.4, 113.9, 126.7, 128.2, 129.8, 135.3, 138.2, 169.0, 170.4. Ms: 331 ((M+1)$^+$, <1), 312 (<1), 273 (14), 255 (4), 229 (66), 201 (3), 151 (12), 105 (100), 77 (32), 51 (3), 42 (5), 28 (4), 18 (1). Anal. Calcd for $C_{19}H_{26}N_2O_3$· C 69.06, H 7.93, N 8.48; found: C 69.35, H 7.90, N 8.38

(1'*S*)-**31b**: R_f = 0.31 (*n*-hexane/ethyl acetate, 1.2). mp 145-146°C. $[\alpha]_D$ = +225.6° (c = 0.18, $CHCl_3$). Ir ($CHCl_3$): 3395br, 3010m, 2975m, 1650s, 1625s, 1485w, 1395s, 1335s, 1155w, 1090w, 905w, 630m. ^{1}H-Nmr: 1.09 (s, *t*-Bu); 1.21 (d, J = 6.2, CH_3-C(1')); 3.00 (d, J = 7.5, H-C(5)); 3.17 (s, NCH_3); 4.14 (m, H-C(1')); 4.77 (br s, $w_{1/2} \approx$ 10, H-olef.), 4.90-5.10 (br, OH); 5.02 (s, H-C(2)); 5.63 (br s, $w_{1/2} \approx$ 10, H-olef.); 7 33-7.45 (m, 5 arom. H). ^{13}C-Nmr: 22.4, 27.3, 38 4, 40.5, 53.4, 70 2, 77.1, 112.4, 116.9, 127.7, 128.6, 130.3, 135.8, 169.7, 171.5 Ms: 312 ((M-18)$^+$, <1), 284 (<1), 273 (1), 255 (3), 241 (1), 229 (33), 186 (7), 124 (4), 105 (100), 77 (22), 51 (3), 42 (9), 29 (12), 18 (29). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C 69.06, H 7.93, N 8.48; found: C 69.04, H 8 23 N, 8.28.

*1-Benzoyl-2(*S*)-*tert*-butyl-3-methyl-5(*S*)-[1'(*R*)-hydroxybut-2-enyl]-6-methylenedihydropyrimidin-4-one* [(1'*R*)-**32**]. Following the general procedure described above for aldol (dienolate) reactions, with 0.11 ml (1.3 mmol, 1.3 eq.) of crotonaldehyde, at -105°C, and with a reaction time of 2 h. The crude product (0.39 g, red-brown) was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:2) to afford 0.20 g (0.56 mmol, 56% yield) of pure (1'*R*)-**32**. R_f = 0.42 (*n*-hexane/ethyl acetate, 1:3). mp 147-148°C. $[\alpha]_D$ = +208.6° (c = 0.26, $CHCl_3$). Ir ($CHCl_3$): 3425 br, 3005m, 2970m, 1670m, 1625s, 1485m, 1445m, 1405s, 1330s, 1085m, 1025m, 970m, 890m, 650w. ^{1}H-Nmr: 1.01 (s, *t*-Bu); 1.68 (d, J = 6.4, CH_3-C(3')); 3.12 (s, NCH_3); 3.46 (br d, $w_{1/2} \approx$ 6, H-C(5)); 4.45-4.67 (br m, H-C(1'), OH); 5.04-5.17 (2 br s, H-C(2), H(olef.)C-C(6)); 5.29 (br s, $w_{1/2} \approx$ 10, H(olef.)C-C(6)); 5.50 (dd, J_1 = 15.5, J_2 = 5.6, H-C(2)); 5.81 (dq, J_1 = 15.5, J_2 = 6.4, H-C(3')); 7.32-7.51 (m, 5 arom. H). ^{13}C-Nmr: 18.1, 27.2, 37.8, 41.2, 51.9, 77.0, 77.5, 113.8, 127.6, 128.7, 129.8, 129.9, 130.6, 135.8, 138.7, 169.4, 171.1 Ms: 256 (M$^+$, <1), 312 (<1), 273 (14), 255 (4), 229 (66), 201 (3), 151 (12), 105 (100), 77 (32), 51 (3), 42 (5), 28 (4), 18 (1). Anal. Calcd for $C_{21}H_{28}N_2O_3$ C 70.76, H 7.92, N 7.86; found: C 70.84, H 8.19, N 7.66.

ACKNOWLEDGEMENTS

We gratefully acknowledge professional help and advice from Dr. V. Gramlich (crystallography), W. Businger (high pressure laboratory), B. Brandenberger (NMR service division), and A. K. Beck (layout of this paper). The sabbatical leave from México and research year at ETH of E. Juaristi was financed by support from the *Schweizerischer Nationalfonds* (Project No. 20-30770.91) and the *SANDOZ AG* (Basel).

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Received, 31st January, 1994