gave 14.4 mg of pure 1: ^{1}H NMR ($CDCl_3$) δ 4.61 (m, 1 H), 4.59 (quintet, J = 1.4 Hz, 1 H), 2.32 (ddd, J = 14.4, 2.4, and 1 Hz), 2.08 (d, J = 14.4 Hz, 1 H), 1.97 (sextet, J = 7.2 Hz, 1 H), 1.90–1.68 (m, 10 H), 1.07 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 162.23, 100.64, 54.76, 49.36, 47.99, 42.80, 41.66, 40.42, 34.54, 30.27, 24.19, 24.00, 23.40, 17.98.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds 1–7, 15, and 17 (17 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of 1,3-Amino Alcohols and 1,3-Amino Ketones

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syn,anti-N-Alkyl-1,3-amino alcohols **2** with three chiral centers are synthesized with high stereoselectivity by reduction of the corresponding *anti-N*-acylamino ketones **1** with $LiAlH_4/TiCl_4$. The intermediate *N*-acylamino alcohols **3** can be isolated when $DIBALH/ZnCl_2$ is used instead of the prior reducing system. Cyclic models are proposed to explain the steric course of the reaction in both cases. On the other hand, hydrolysis of tetrahydropyrimidines **8** with 1 N HCl at 25 °C leads to *syn*-1,3-amino ketones **9** with high stereoselectivity. Several reducing reagents and conditions are tested in the conversion of *syn*-**9** into the subsequent 1,3-amino alcohols. $DIBALH/ZnCl_2$ gives the best results in the last reaction leading to *syn,syn*-1,3-amino alcohols **10** as practically a single diastereoisomer.

Introduction

Among 1,3-difunctionalized compounds, the 1,3-amino alcohol fragment is one of the most important target structures because of the pharmacology of these substances and because this functionality is found in several antibiotics[1] and other biologically active natural products.[2] Therefore, the synthesis of these molecules has been of great interest,[1a,3] and several reduction methods have been widely used for this purpose.[4,5] In this context, preparation of 1,3-amino alcohols by reduction of β-amino carbonyl compounds is the most frequently employed methodology.[4,6]

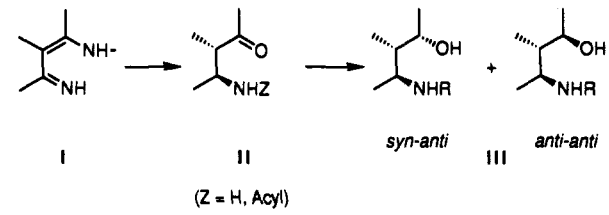
In our research group 4-amino-1-aza 1,3-dienes I have been used as starting materials for several 1,3-difunctionalized compounds like 1,3-amino ketones[7] and 1,3-diamines.[7a] The former have two chiral centers in the molecule and are obtained with high stereoselectivity as mixtures of two diastereoisomers from which only the anti isomer (the major component) could be isolated (II in Scheme I). We reported diastereo-[7b] and enantioselective[8] synthesis of 1,3-amino alcohols III with three chiral centers by reduction of 1,3-amino- and 1,3-amido ketones II. In this synthesis the syn,anti and anti,anti diastereoisomers were obtained (Scheme I).

The reduction of 1,3-amino ketones II is highly stereoselective only with unsubstituted amino ketones (Z = H) which give the syn,anti isomer as the major product. The stereoselectivity sensibly decreases for *N*-acylamino ketones (II, Z = Acyl).[7b] In this paper we report our studies to improve the diastereoselective synthesis of 1,3-amino alcohols having three chiral centers from *anti-N*-acyl-1,3-amino ketones[9] and to the synthesis of *syn*-1,3-amino ketones and the subsequent 1,3-amino alcohols.

Results and Discussion

Synthesis of *N*-Alkyl-1,3-amino Alcohols 2. (A) Reduction of *anti*-1,3-Amino Ketones 1 with $LiAlH_4/TiCl_4$. In our preliminary work on the synthesis of 1,3-amino alcohols, as pointed out above, we obtained low-to-moderate diastereoselectivities when *N*-acylamino ketones were used with $LiAlH_4$ as reducing agent. In order to improve the stereoselectivity in the reduction process,

Scheme I



Scheme II

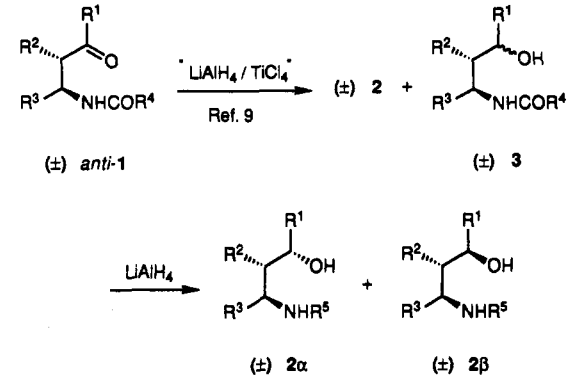


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Table I. 1,3-Amino Alcohols 2 Obtained by Reduction of *anti*-*N*-Acyl-1,3-amino Ketones 1 (Scheme II)

entry	compd[a]	R^3	R^4	R^5	2α:2β[b,c]	yield[b,d] (%)
1	**2a**	Ph	*p*-ClC_6H_4	*p*-$ClC_6H_4CH_2$	>99:1 (50:50)	94 (74)
2	**2b**	Ph	Ph	$C_6H_5CH_2$	97:3 (40:60)	92 (80)
3	**2c**	Ph	*p*-MeC_6H_4	*p*-$MeC_6H_4CH_2$	95:5 (44:56)	90 (72)
4	**2d**	Ph	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4CH_2$	96:4 (64:36)	95 (70)
5	**2e**	Ph	Me	Et	90:10 (77:23)	80 (62)
6	**2f**	Ph	EtO	Me	94:6 (61:39)	85 (69)
7	**2g**	*p*-MeC_6H_4	Ph	$C_6H_5CH_2$	95:5 (38:62)	88 (72)
8	**2h**	*c*-C_6H_{11}	Ph	$C_6H_5CH_2$	94:6 (74:26)	86 (71)

[a] R^1 = Ph, R^2 = Me. [b] By ^1H NMR (300 MHz) of the crude residue (estimated error ≤±2). [c] In parentheses, values obtained by reduction of *anti*-1 with $LiAlH_4$/THF (ref 7b). [d] In parentheses, yield of isolated product 2α based on *anti*-1.

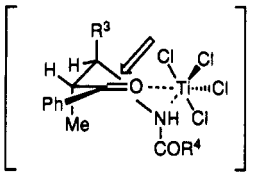
Table II. *N*-Acyl-1,3-amino Alcohols 3 and 1,3-Amino Alcohols 2 Obtained from *anti*-1 (Scheme III)

entry	compd[a]	R^4	3α:3β[b]	yield[b,c] (%)	2α:2β[b]	yield[b] (%)
1	**a**	*p*-ClC_6H_4	88:12	95 (79)	86:14	93
2	**b**	Ph	98:2	93 (80)		91[d]
3	**c**	*p*-MeC_6H_4	88:12	91 (70)	89:11	92
4	**d**	*p*-$MeOC_6H_4$	89:11	94 (80)	92:8	93
5	**e**	Me	>99:1	97 (84)		92[d]
6	**f**	EtO	*e*		68:32 (61:39)[f]	95
7	**f**	^{t}BuO	*e*		50:50	93

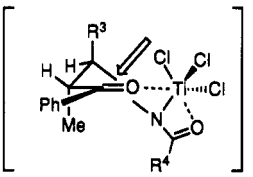
[a] R^1 = R^3 = Ph, R^2 = Me. [b] By ^1H NMR (300 MHz) of the crude residue (estimated error ≤±2). [c] In parentheses, yields of isolated products, 3α. [d] By reduction of isolated 3α. [e] Unidentified mixture. [f] By direct reduction of *anti*-1 (R^4 = EtO) with $LiAlH_4$/THF (see ref 7b).

we decided to use a chelating agent as $TiCl_4$[10] to ensure that the reaction takes place through a rigid cyclic intermediate to give predominantly *syn,anti*-amino alcohols.[7b] Thus, in a previous paper[9] we reported the reduction of *anti*-*N*-acyl-1,3-amino ketones **1** to 1,3-amino alcohols **2** in two steps using $LiAlH_4/TiCl_4$. *syn,anti*-1,3-Amino alcohols 2α were obtained as major compounds with high diastereoselectivity[11] (Scheme II, Table I).

To explain the steric course of the process two cyclic models, **4** and **5**, were proposed with the hydride attacking from the less hindered side.



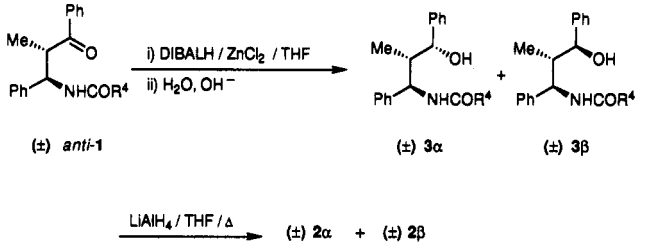
4



5

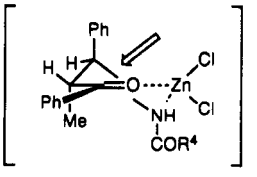
(B) Reduction of *anti*-1,3-Amino Ketones 1 with DIBALH/$ZnCl_2$. In order to isolate the *N*-acyl-1,3-amino alcohols **3**, the reaction was carried out with smaller amounts of $LiAlH_4$ (ratio *anti*-1:$LiAlH_4$ = 1:1.5–2); however, compound **3** was isolated in only two cases (**2b** and **2d**). In most cases, variable amounts of the starting material were recovered. Thus, we investigated the use of a more selective reducing agent than $LiAlH_4$, like DIBALH, in presence of $ZnCl_2$ as chelating agent.[12]

Scheme III



The reaction was performed with *anti*-1 (R^1 = R^3 = Ph, R^2 = Me) in THF at −78 °C (ratio *anti*-1:$ZnCl_2$:DIBALH = 1:3:6)[13] for sevral hours to give compounds **3** as mixtures of two diastereoisomers α and β with high stereoselectivity (Scheme III, Table II, entries 1–5). Compound 3α was isolated by crystallization from the crude residue.

The structural assignments of compounds **3** were initially based on their ^1H NMR spectra, and they were confirmed by reduction of the crude residues or the major epimer (3α) with $LiAlH_4$ to give the corresponding 1,3-amino alcohols **2** previously described (Scheme III, Table II). These results can be understood considering that, as in the case of $TiCl_4$, $ZnCl_2$ coordinates with the nitrogen and the carbonyl oxygen forming complex **6** which favors the attack of the hydride from the less hindered side.



6

In attempts to isolate 1,3-amino alcohols **3** we observed rather different behavior of compounds *anti*-1 (R^4 = alkoxy group) related to that shown by *anti*-1 (R^4 = alkyl, aryl).

(6) (a) Samaddar, A. K.; Konar, S. K.; Nasipuri, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1449. (b) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1213. (c) Oszbach, G.; Neszmélyi, A. *Liebigs Ann. Chem.* **1990**, 211.

(7) (a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255. (b) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052.

(8) Barluenga, J.; Olano, B.; Fustero, S.; Foces-Foces, M. C.; Hernández, F. J. *J. Chem. Soc., Chem. Commun.* **1988**, 410.

(9) Preliminary account: Barluenga, J.; Aguilar, E.; Olano, B.; Fustero, S. *Synlett* **1990**, 463.

(10) We had used this Lewis acid with success in the synthesis of syn,syn diols starting from 1,3-diketones: Barluenga, J.; Resa, J.; Resa, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425.

(11) Attempts to obtain the diastereoisomer 2β as the major one were unsuccessful using other reducing agents (e.g., $LiAlH(O^tBu)_3$/THF, see ref 10). Nevertheless, this problem has been overcome in our research group by epimerization of carbynol carbon in isomer α, see ref 7b.

(12) DIBALH/$ZnCl_2$ has been used with success in the stereoselective reduction of β-keto sulfoxides: Carreño, M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodríguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.

(13) The use of higher excesses of DIBALH (*anti*-1:DIBALH = 1:20) led to similar results but lower ratios *anti*-1:DIBALH (e.g., = 1:3) gave lower chemical yields.

Table III. 1,3-Amino Ketones 9 Obtained from Tetrahydropyrimidines 8 (Scheme IV)

entry	acid	R	time (h)	temp (°C)	ratio[a] syn:anti	yield[a] (%)
1	1 N HCl	p-MeC_6H_4	1	25	93:7	99
2	1 N HCl	Ph	1	25	92:8	98
3	H_2O/p-$TolSO_3H$ cat.	Ph	2	80	72:28	97
4	H_2O/AcOH (20%)	Ph	2	80	47:53	96

[a] By ^1H NMR (300 MHz) (estimated error ≤±2).

Table IV. 1,3-Amino Alcohols 10 Obtained by Reduction of *syn*-1,3-Amino Ketone 9 (R = Ph) (Scheme V)

entry	reducing agent[a]	Lewis acid	solvent	temp (°C)	time (h)	ratio[b] syn,syn:anti,syn	yield[b] (%)
1	DIBAL	$ZnCl_2$	THF	−78	3	>99:1	95
2	DIBAL		toluene	−78	3	60:40	87
3	TBH	$ZnCl_2$	THF	25	3	90:10	90
4	TBH		THF	−78	5	86:14	93
5	TBH		THF	25	14	80:20	95
6	$LiAlH_4$	LiCl	THF	25	4	83:17	96
7	$LiAlH_4$		THF	25	14	69:31	96
8	$NaBH_4$		MeOH/THF (1:1)	25	3	70:30	87
9	Red-Al		toluene	25	14	46:54	90
10	Red-Al	NaBr	toluene	25	3	43:57	95
11	Red-Al		toluene	−78	3	37:63	94

[a] TBH = $LiAlH(O^tBu)_3$, Red-Al = $NaAlH_2(OCH_2CH_2OCH_3)_2$. [b] By ^1H NMR (300 MHz) (estimated error ≤±2).

Thus, when the reaction was carried out with *anti*-1 (R^1 = R^3 = Ph, R^2 = Me, R^4 = EtO, ^{t}BuO) and DIBALH/$ZnCl_2$/THF in the conditions described above, we were unable to detect the corresponding *N*-(alkoxycarbonyl)-1,3-amino alcohols. Further reduction of the uncharacterized mixture led to 1,3-amino alcohol **2f** as a mixture of both epimers α and β but, in this case, with low diastereoselectivity (Scheme III, Table II, entries 6 and 7). One possible explanation for these values could be the participation of intermediates different from **6**, probably due to the chelation of the carbamate carbonyl group with the Lewis acid favoring open chain or larger cyclic structures, with a consequent lowering in the stereoselectivity.

Synthesis of *syn*-1,3-Amino Ketones 9 and the Corresponding 1,3-Amino Alcohols 10. All of the methodology reported by us to date has referred to the reduction of *anti*-1,3-amino ketones leading to *anti,anti*- and especially *syn,anti*-amino alcohols. Our purpose at the moment is to obtain the other two diastereoisomeric 1,3-amino alcohols, that is the syn,syn and the anti,syn isomers. For this purpose, we have to prepare *syn*-1,3-amino ketones.

We had already obtained *anti*-1,3-amino ketones by hydrolysis of tetrahydropyrimidines.[8] That prompted us to try the synthesis of the syn epimers by changing the hydrolysis conditions. To perform a conditions-test, we submitted the racemic tetrahydropyrimidines 8 (obtained from 4-amino-1-azadienes 7)[8] to several conditions of hydrolysis, obtaining 1,3-amino ketones 9 as mixtures of two epimers *anti*-9 and *syn*-9 with different ratios (Scheme IV, Table III).

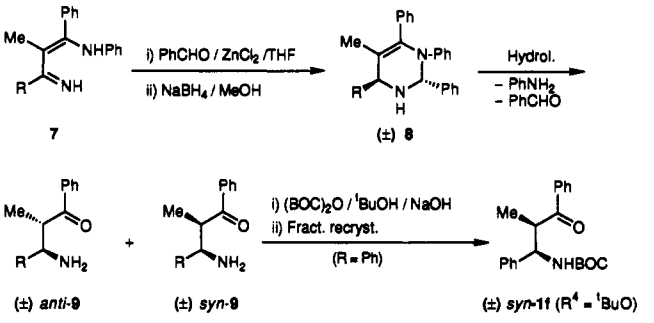
From the prior results we conclude that aqueous 1 N HCl at 25 °C are the conditions of choice to obtain *syn*-1,3-amino ketones. The configurational assignment and ratio determination of 9 was made from ^1H NMR spectra of the crude mixture,[7a,8] and the isolation of the syn isomer was carried out by conversion of the mixture into the corresponding *N*-BOC derivatives followed by recrystallization and deprotection with TFA (Scheme IV).

Aiming at the completion of the synthesis of 1,3-amino alcohols with three chiral centers, we carried out the reduction of *syn*-9 (R = Ph) with several reducing reagents to give the epimeric 1,3-amino alcohols 10 in different ratios with very good yields (Scheme V, Table IV).

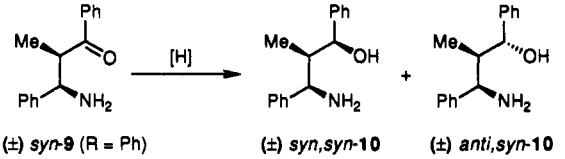
Considering the data displayed in the list, we must conclude that, as in previous experiments with *anti*-1,3-amino ketones, there is a preference for the formation of the syn relative stereochemistry in the creation of the carbynolic center, the syn,syn epimer being the major diastereoisomer in most of the cases (Table IV, entries 1–8). Nevertheless, $LiAlH_4$/THF which had given good results in the reduction of *anti*-amino ketones[7b] surprisingly led only to a moderate stereoselectivity in the reduction of their syn epimer (Table IV, entry 7); the best results in this case were obtained with DIBALH/$ZnCl_2$ which gave the syn, syn epimer exclusively (Table IV, entry 1). As expected,[7b] the anti,syn isomer was obtained with moderate stereoselectivities (Table IV, entries 9–11), Red-Al/toluene/−78 °C being the best conditions to obtain this isomer (Table IV, entry 11).[14]

Our current interest is directed toward the synthesis of the 1,3-amino alcohol units present in several natural products showing antibiotic activity.[16]

Scheme IV



Scheme V



(14) Other reducing agents like $LiAlH_4/TiCl_4/CH_2Cl_2$ or $Me_4NBH(OAc)_3$[15] failed. N-unsubstituted 1,3-amino ketones decompose in presence of these reagents to give unidentified products.

(15) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, 5939.

In conclusion, a highly stereoselective synthesis of N-substituted 1,3-amino alcohols with three chiral centers has been described. Convenient methodology for the stereoselective preparation of *syn*-1,3-amino ketones and the corresponding 1,3-amino alcohols has been also established in this paper.

Experimental Section

General. All reagents were of commercial quality (Aldrich). Solvents as THF, CH_2Cl_2, and toluene were dried and distilled upon standard procedures before use. Solvents used in extractions were distilled prior to use. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 or 75 MHz, respectively. Mass spectra were obtained by EI (70 eV). Melting points were determined in open capillaries and are uncorrected.

Preparation of compounds *anti*-**1a–h** was carried out according to a previously described procedure.[7a] Spectral data, physical constants, and microanalyses of *anti*-**1a–c, e–g, 2a–c, e–g**, and *anti*-**9** have been previously reported.[7]

Data for compounds *anti*-**1d**, *anti*-**1f** (R^4 = ^{t}BuO), and *anti*-**1h**, preparation of compounds **2**, and data for **2d** and **2h** are included as supplementary material.

Preparation of the *N*-Acyl-1,3-amino Alcohol 3a (Representative Procedure). To a solution of *anti*-**1a** (1.89 g, 5 mmol) in anhydrous THF (20 mL) was added anhydrous $ZnCl_2$ (2.04 g, 15 mmol) in an ice bath under inert atmosphere, and the solution was stirred for 2 h. DIBALH (30 mmol, 20% in *n*-hexane) in anhydrous THF (20 mL) was added at −78 °C, and stirring was continued for 3 h. Anhydrous MeOH (15 mL) was added at −78 °C and, when the evolution of gas was complete, aqueous 3 N NaOH (25 mL) was added. The organic layer was extracted with ether (2 × 25 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give 1.88 g (95%) of crude **3a**. This residue was stirred with *n*-hexane (6 mL) and filtered to get 1.50 g (79%) of isomer **3a**α as a white solid. After evaporation and treatment (3 × 5 mL) with *n*-hexane, 0.22 g of a **3a**β enriched mixture (ratio **3a**α:**3a**β − 20:80) was obtained from the filtrate.

(1*R,2*S**,3*R**)-3-[(*p*-Chlorobenzoyl)amino]-2-methyl-1,3-diphenyl-1-propanol (3aα).** Mp: 158–60 °C (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.83 (d, 3 H, J = 6.9 Hz), 2.23 (m, 1 H), 4.88 (br s, 1 H), 5.25 (br t, 1 H), 7.2–7.8 (m, 14 H_{arom}). ^{13}C NMR: δ 166.8 (s), 156.3 (s), 144.2 (s), 141.8 (s), 128.8–125.3 (m), 72.5 (d), 58.3 (d), 45.1 (d), 10.6 (q). MS: m/e 379 (M^+, <3), 139 (100). Anal. Calcd for $C_{23}H_{22}ClNO_2$: C, 72.72; H, 5.84; N, 3.69. Found: C, 72.70; H, 5.89; N, 3.61.

(1*S,2*S**,3*R**)-3-[(*p*-Chlorobenzoyl)amino]-2-methyl-1,3-diphenyl-1-propanol (3aβ).** ^1H NMR: δ 0.71 (d, 3 H, J = 6.9 Hz), 2.40 (m, 1 H), 4.56 (d, 1 H, J = 7.9 Hz), 5.01 (br t, 1 H), 7.2–7.9 (m, 14 H_{arom}).

Yields and diastereoisomer ratios for compounds **3** are listed in Table II.

(1*R,2*S**,3*R**)-3-(Benzoylamino)-2-methyl-1,3-diphenyl-1-propanol (3bα).** Mp: 168–71 °C (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.80 (d, 3 H, J = 6.9 Hz), 2.22 (m, 1 H), 3.9 (br s, 1 H, OH), 4.90 (br s, 1 H), 5.25 (br t, 1 H), 7.1–7.8 (m, 15 H_{arom}). ^{13}C NMR: δ 167.6 (s), 1 (s), 141.2 (s), 134.1 (s), 131.6–125.4 (m), 72.2 (d), 58.2 (d), 45.2 (d), 10.3 (q). MS m/e 345 (M^+, <3.3), 105 (100). Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.06. Found: C, 79.89; H, 6.73; N, 3.93.

(1*S,2*S**,3*R**)-3-(Benzoylamino)-2-methyl-1,3-diphenyl-1-propanol (3bβ).** Obtained as a mixture together with **3b**α (ratio **3b**α:**3b**β = 32:68). ^1H NMR: δ 0.52 (d, 3 H, J = 6.9 Hz), 2.44 (m, 1 H), 4.48 (d, 1 H, J = 7.9 Hz), 4.95 (br t, 1 H), 7.0–7.7 (m, 15 H_{arom}).

(1*R,2*S**,3*R**)-2-Methyl-3-[(*p*-methylbenzoyl)amino]-1,3-diphenyl-1-propanol (3cα).** Mp: 159–61 °C (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.75 (d, 3 H, J = 7.1 Hz), 2.23 (m, 1 H), 2.41 (s, 3 H), 3.93 (br s, 1 H, OH), 4.95 (br s, 1 H), 5.23 (br t, 1 H), 7.0–7.8 (m, 14 H_{arom}). ^{13}C NMR: δ 167.7 (s), 143.1 (s), 142.0 (s), 141.3 (s), 131.2 (s), 129.2–125.4 (m), 71.2 (d), 58.1 (d), 45.3 (d), 21.4 (q), 10.2 (q). MS m/e 359 (M^+, <4), 119 (100). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.30; H, 7.13; N, 3.85.

(1*S,2*S**,3*R**)-2-Methyl-3-[(*p*-methylbenzoyl)amino]-1,3-diphenyl-1-propanol (3cβ).** Obtained as a mixture together with **3c**α (ratio **3c**α:**3c**β = 45:55). ^1H NMR: δ 0.54 (d, 3 H, J = 7.0 Hz), 2.36 (s, 3 H), 2.43 (m, 1 H), 4.51 (d, 1 H, J = 7.9 Hz), 4.93 (br t, 1 H), 7.0–7.6 (m, 14 H_{arom}).

(1*R,2*S**,3*R**)-2-Methyl-3-[(*p*-methoxybenzoyl)amino]-1,3-diphenyl-1-propanol (3dα).** Mp: 160 °C dec (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.78 (d, 3 H, J = 7.1 Hz), 2.21 (m, 1 H), 3.62 (br s, 1 H, OH), 3.82 (s, 3 H), 4.89 (br s, 1 H), 5.25 (br t, 1 H), 6.9–7.9 (m, 14 H_{arom}). ^{13}C NMR: δ 167.2 (s), 162.2 (s), 143.2 (s), 141.4 (s), 128.9–125.4 (m), 72.1 (d), 58.1 (d), 55.3 (q), 45.2 (d), 10.3 (q). MS m/e 357 (M^+, <3), 135 (100). Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.90; H, 6.73; N, 3.85.

(1*S,2*S**,3*R**)-2-Methyl-3-[(*p*-methoxybenzoyl)amino]-1,3-diphenyl-1-propanol (3dβ).** Obtained as a mixture together with **3d**α (ratio **3d**α:**3d**β = 50:50). ^1H NMR: δ 0.57 (d, 3 H, J = 6.9 Hz), 2.52 (m, 1 H), 3.75 (s, 3 H), 4.62 (d, 1 H, J = 7.9 Hz), 5.07 (br t, 1 H), 6.8–7.6 (m, 14 H_{arom}).

(1*R,2*S**,3*R**)-3-Acetamido-2-methyl-1,3-diphenyl-1-propanol (3eα).** Mp: 120–3 °C (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.65 (d, 3 H, J = 7.1 Hz), 2.03 (s, 3 H), 2.15 (m, 1 H), 4.09 (br s, 1 H, OH), 4.85 (br s, 1 H), 4.98 (dd, 1 H, J = 8.7 and 10.6 Hz), 6.87 (d, 1 H, J = 10.6 Hz), 7.1–7.4 (m, 10 H_{arom}); ^{13}C NMR δ 164.4 (s), 141.8 (s), 139.3 (s), 130.3–125.4 (m), 70.9 (d), 55.1 (d), 45.1 (d), 23.2 (q), 10.1 (q). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.40; N, 4.98.

Reduction of *N*-Acyl-1,3-amino Alcohols 3 with $LiAlH_4$/THF (General Procedure). To a stirred slurry of $LiAlH_4$ (0.76 g, 20 mmol) in anhydrous THF (25 mL) was added a solution of **3** or **3**α (5 mmol) in anhydrous THF (10 mL) dropwise in an ice bath, and the mixture was refluxed during 4 h. After usual workup with anhydrous MeOH and aqueous 3 N NaOH, as described above, 1,3-amino alcohols **2** were obtained as a mixture of two diastereoisomers **2**α and **2**β. Yields and diastereoisomer ratios are listed in Table II.

Preparation of the Tetrahydropyrimidine 8 (R = Ph) (General Procedure).[8] Anhydrous $ZnCl_2$ powder (2.73 g, 20 mmol) was added to a solution of **7** (R = Ph)[18] (6.24 g, 20 mmol) and benzaldehyde (2.12 g, 20 mmol) in anhydrous THF (40 mL) in an ice bath. The solution was refluxed overnight and then treated with aqueous 3 N NaOH (40 mL) and extracted with ether. The organic layer was dried, filtered, and evaporated, and the crude residue (the corresponding 1,2-dihydropyrimidine[8]) was dissolved, without further purification, in MeOH (40 mL) and treated with $NaBH_4$ (2.28 g, 60 mmol) in MeOH (30 mL) at rt overnight. The solvent was evaporated under reduced pressure, and ether (50 mL) and aqueous 3 N NaOH (40 mL) were added to the slurry. After the usual workup, the remaining syrup was stirred with MeOH (10 mL) to give 5.60 g (70%) of chromatographically pure **8** (R = Ph) as a white solid.

(2*R,6*S**)-5-Methyl-2,3,4,6-tetraphenyl-1,2,3,6-tetrahydropyrimidine (8, R = Ph).** Mp: 138–40 °C (*n*-hexane–$CHCl_3$ (6:1)); IR (Nujol) 3300, 1580 cm^{-1}; ^1H NMR: δ 1.40 (s, 3 H), 2.12 (br s, 1 H, NH), 4.23 (s, 1 H), 5.72 (s, 1 H), 6.6–8.1 (m, 20 H_{arom}). ^{13}C NMR: δ 148.8 (s), 142.3 (s), 140.9 (s), 137.6 (s), 136.2 (s), 129.8–121.7 (m), 120.7 (s), 77.0 (d), 59.1 (d), 17.5 (q). MS m/e 402 (M^+, 19), 296 (100), 193 (68). Anal. Calcd for $C_{29}H_{26}N_2$: C, 86.57; H, 6.47; N, 6.97. Found: C, 86.47; H, 6.45; N, 7.06.

(2*R,6*S**)-5-Methyl-2,3,4-triphenyl-6-*p*-tolyl-1,2,3,6-tetrahydropyrimidine (8, R = *p*-Tolyl).** Yield: 6.41 g (77%). Mp: 120–23 °C (*n*-hexane–$CHCl_3$ (6:1)). ^1H NMR: δ 1.35 (s, 3 H), 2.12 (br s, 1 H, NH), 2.28 (s, 3 H), 4.19 (s, 1 H), 5.67 (s, 1 H), 6.7–8.0 (m, 19 H_{arom}). ^{13}C NMR: δ 148.8 (s), 140.9 (s), 139.1 (s), 137.5 (s), 137.0 (s), 135.9 (s), 130.3–121.7 (m), 120.9 (s), 76.8 (d), 58.7 (d), 21.0 (q), 17.4 (q). Anal. Calcd for $C_{30}H_{28}N_2$: C, 86.50; H, 6.77; N, 6.73. Found: C, 86.37; H, 6.80; N, 6.80.

(16) Work is in progress in our laboratory in order to achieve the N-terminal amino acids of nikkomycins[17] in an enantioselective manner. Viado, A. L. Ph.D. Thesis in progress.

(17) (a) Hahn, H.; Heitsch, H.; Rathmann, R.; Zimmermann, G.; Bormann, C.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1987**, 803. (b) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 5818 and references cited therein.

(18) Hoberg, H.; Barluenga, J. *Synthesis* **1970**, 142.

Hydrolysis of Tetrahydropyrimidines 8 (General Procedure). To a solution of tetrahydropyrimidine 8 (10 mmol) in THF (10 mL) was added the acidic aqueous solution (30 mL) at rt. The mixture was stirred under time and temperature conditions described in Table III. The solution was washed twice with ether (25 mL), and the aqueous layer was treated with aqueous 3 N NaOH until basic and extracted with ether (2 × 25 mL). The organic layer was worked up as usual to give 1,3-amino ketones **9** as a mixture of two diastereoisomers. Yields and diastereoisomer ratios are listed in Table III.

Isolation of Diastereoisomer *syn*-9 (R = Ph). (A) Preparation of *N*-BOC Derivative *syn*-1f (R^4 = ^{t}BuO). ^{t}BuOH/H_2O (1:1, 20 mL) and NaOH (0.44 g, 11 mmol) were added in an ice bath to 2.41 g of crude **9** (R = Ph) obtained upon the former procedure following the conditions listed on Table III (entry 2). To this solution was added $(BOC)_2O$ (2.4 g, 11 mmol) at rt with stirring. The resulting mixture was stirred at rt for 14 h, and the excess of $(BOC)_2O$ was extracted with AcOEt (25 mL). The aqueous layer was treated with aqueous $KHSO_4$ (2.24 g $KHSO_4$ in 15 mL H_2O) and extracted with AcOEt (2 × 25 mL). After usual workup 3.42 g of crude **1f** (R^4 = ^{t}BuO) was obtained. After recrystallization (*n*-hexane–$CHCl_3$ (3:1)) 2.33 g (70%) of *syn*-**1f** (R = ^{t}BuO) was isolated.

(2*R,3*R**)-3-[(*tert*-Butoxycarbonyl)amino]-2-methyl-1,3-diphenyl-1-propanone (*syn*-1f, R = ^{t}BuO).** Mp: 138–40 °C. IR (KBr) 3350, 1663, 1511 cm^{-1}. ^1H NMR: δ 1.08 (d, 3 H, *J* = 7.5 Hz), 1.40 (s, 9 H), 4.01 (m, 1 H), 4.98 (br s, NH), 5.12 (br s, 1 H), 7.1–7.9 (m, 10 H_{arom}). ^{13}C NMR: δ 201.7 (s), 155.2 (s), 139.9 (s), 136.4 (s), 133.0–126.6 (m), 77.1 (s), 56.2 (d), 46.1 (d), 28.2 (q), 13.1 (q); MS *m/e* 339 (M^+, <3.5), 106 (76), 57 (100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.33; H, 7.29; N, 4.18.

(B) Deprotection of *N*-BOC Derivative *syn*-1f (R^4 = ^{t}BuO). TFA (35 mmol) in CH_2Cl_2 (10 mL) was added to a solution of *syn*-**1f** (R^4 = ^{t}BuO, 2.33 g, 6.9 mmol) in CH_2Cl_2 (10 mL) at rt. After the solution was stirred for 2 h, the solvent was evaporated and aqueous 3 N NaOH (25 mL) and CH_2Cl_2 (25 mL) were added. The organic layer was worked up to give 1.71 g (quantitative) of *syn*-**9** (R = Ph) as a viscous oil which decomposes during distillation or chromatographic purification.

(2*R,3*R**)-3-Amino-2-methyl-1,3-diphenyl-1-propanone (*syn*-9, R = Ph).** IR (film): 3345, 1690 cm^{-1}. ^1H NMR: δ 1.18 (d, 3 H, *J* = 7.1 Hz), 1.70 (br s, 2 H, NH_2), 3.75 (m, 1 H), 4.44 (d, 1 H, *J* = 5.7 Hz), 7.1–7.9 (m, 10 H_{arom}). ^{13}C NMR: δ 203.0 (s), 143.8 (s), 136.0 (s), 132.4–126.2 (m), 56.4 (d), 47.6 (d), 11.8 (q).

(2*R,3*R**)-3-Amino-2-methyl-1-phenyl-3-*p*-tolyl-1-propanone (*syn*-9, R = *p*-Tolyl).** Not isolated, data obtained from a syn/anti mixture (ratio syn:anti = 93:7). IR (film): 3340, 1685 cm^{-1}. ^1H NMR: δ 1.28 (d, 3 H, *J* = 7.0 Hz), 2.32 (s, 3 H), 2.73 (br s, 2 H, NH_2), 3.79 (m, 1 H), 4.43 (d, 1 H, *J* = 5.7 Hz), 7.2–8.1 (m, 9 H_{arom}). ^{13}C NMR: δ 203.4 (s), 140.9 (s), 136.3 (s), 136.2 (s), 132.6–126.3 (m), 56.3 (d), 47.9 (d), 20.7 (q), 12.1 (q).

Reduction of *syn*-9 (R = Ph) (General Procedure). To a solution of *syn*-**9** (R = Ph) (1.0 g, 4.2 mmol) in the corresponding solvent (30 mL) was added the reducing agent (25.2 mequiv) at the cited temperature, and the mixture was stirred for several hours (see Table IV). In those cases in which a Lewis acid (anhydrous $ZnCl_2$ or NaBr powder, 12.6 mequiv; anhydrous LiCl powder, 6.3 mequiv) was used, it was added 15 min before the reducing agent. The reaction mixture was quenched with 3 N NaOH (25 mL) and extracted with ether (2 × 25 mL). After usual workup, 1,3-amino alcohol **10** was obtained as a mixture of two diastereoisomers. Yields and diastereoisomer ratios are listed in Table IV.

(1*S,2*R**,3*R**)-3-Amino-2-methyl-1,3-diphenyl-1-propanol (*syn,syn*-10).** Isolated (0.73 g, 72%) (Table IV, entry 1) by recrystallization of the crude residue (*n*-hexane–$CHCl_3$ (6:1)). Mp: 100–3 °C. ^1H NMR: δ 0.82 (d, 3 H, *J* = 7.0 Hz), 2.03 (m, 1 H), 3.42 (br s, 3 H, OH + NH_2), 4.41 (d, 1 H, *J* = 2.2 Hz), 5.21 (d, 1 H, *J* = 2.0 Hz), 7.1–7.9 (m, 10 H_{arom}). ^{13}C NMR: δ 142.1 (s), 140.6 (s), 128.9–125.2 (m), 77.8 (d), 60.0 (d), 45.4 (d), 13.2 (q); MS *m/e* 241 (M^+, <3.2), 106 (100). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.72; H, 7.91; N, 5.91.

(1*R,2*R**,3*R**)-3-Amino-2-methyl-1,3-diphenyl-1-propanol (*anti,syn*-10).** Isolated (0.53 g, 52%) (Table IV, entry 11) by flash chromatography (*n*-hexane–ether (3:1)) of the crude mixture. Mp: 107–9 °C (*n*-hexane–$CHCl_3$ (3:1)). ^1H NMR: δ 0.65 (d, 3 H, *J* = 7.0 Hz), 2.08 (m, 1 H), 3.98 (br s, 3 H, OH + NH_2), 4.31 (d, 1 H, *J* = 2.2 Hz), 4.72 (d, 1 H, *J* = 7.2 Hz), 7.0–7.8 (m, 10 H_{arom}). ^{13}C NMR: δ 144.4 (s), 140.5 (s), 129.1–123.2 (m), 77.4 (d), 57.1 (d), 44.3 (d), 12.1 (q). MS *m/e* 241 (M^+, <3), 106 (100). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.65; H, 7.97; N, 5.82.

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Supplementary Material Available: Experimental procedures for additional obtained compounds (3 pages). Ordering information is given on any current masthead page.