Diastereoselective Synthesis of γ-Amino Alcohols with Three Chiral Centers by Reduction of β-Amino Ketones and Derivatives

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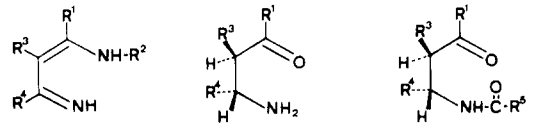
γ-Amino alcohols **4** with three chiral centers are obtained in very good yields by reduction of β-amino ketones **2** and β-acylamino ketones **3** with $LiAlH_4$. The stereochemistry of the two diastereoisomers obtained in the reaction (**4α** and **4β**) is unequivocally set by the stereochemical study of their cyclic derivatives **5** and **8**. The diastereoisomer ratio depends on the reaction conditions and on the N-substituent in the starting substrate. A sequence which includes an $AlCl_3$-promoted isomerization allows us to obtain **4β** from **4α**.

The preparation of γ-amino alcohols **4**,[1] as well as the isolation and stereochemical determination of their diastereoisomers, are important in organic synthesis because of the pharmacology of these products as analgesics[2] and because the γ-amino alcohol unit is very common in natural products.[3]

The most commonly used synthesis of γ-amino alcohols cited in the literature utilizes reduction reactions. Thus, simple γ-amino alcohols can be obtained from enaminones,[4,5] isoxazolines,[3,6-8] and, specifically, β-amino carbonyl compounds.[1,9,10] In the latter case reduction of β-amino ketones with a chiral center in the α or β position is relatively frequent,[1,11] whereas examples of reduction of β-amino ketones with chirality in both positions are limited. In this way Lyapova and co-workers[12] have described a highly stereoselective synthesis of 3-amino-1,2,3-triphenylpropan-1-ols.

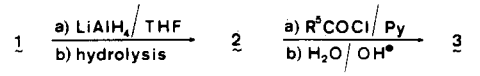
Recently, we have reported[13] that β-amino ketones of type **2** and their *N*-acyl derivatives **3** can be easily obtained by selective reduction of vinylogous amidines **1**.[14,15]



1 **2** **3**

Continuing with our study about the reduction of these systems we describe here the diastereoselective synthesis of γ-amino alcohols **4** by reduction of β-amino ketones **2** and **3** with $LiAlH_4$. The reaction of **4** with carbonic acid derivatives or carbonyl compounds affords cyclic derivatives of which the conformational study gives us convincing data on the relative stereochemistry of starting γ-amino alcohols **4**.

Scheme I



Scheme II

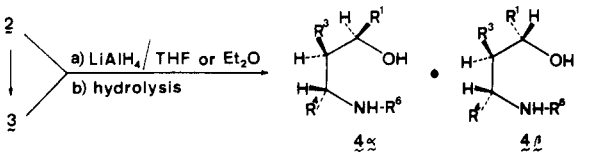


Table I. β-Acylamino Ketones 3[a] Obtained by Reaction of 2 and Acyl Chlorides

3[b]	R^4	R^5	yield, %	mp, °C
a	C_6H_5	CH_3	97[c]	179–181[c]
b	p-$CH_3C_6H_4$	CH_3	90[c]	169–170[c]
c	C_6H_5	$CH(CH_3)_2$	91	167–169
d	C_6H_5	C_6H_{11}	90	184–185
e	C_6H_5	OC_2H_5	83	169–171
f	p-$CH_3C_6H_4$	OC_2H_5	85	120–121
g	C_6H_5	C_6H_5	95	224–226
h	C_6H_5	p-$CH_3C_6H_4$	92	168–170
i	C_6H_5	p-ClC_6H_4	83	149–151
j	p-$CH_3C_6H_4$	C_6H_5	91	190–192

[a] For β-amino ketones **2** see Experimental Section and ref 13. [b] $R^1 = C_6H_5$, $R^3 = CH_3$. [c] See ref 13.

Results and Discussion

I. Reduction of 2 and 3 with $LiAlH_4$. As previously indicated[13] reduction of **1** with $LiAlH_4$ followed by hydrolysis leads in excellent yields to β-amino ketones **2**, which on reaction with acyl chlorides in pyridine easily afford **3** (see Scheme I and Table I).

Reduction of **2** and **3** with an excess of $LiAlH_4$ in THF or ether for several hours gives with high yields γ-amino alcohols **4** as a mixture of diastereoisomers (α and β). The relative ratio of these diastereoisomers has found to be dependent on the nature of R^6 and on the reaction conditions used (see Scheme II and Table II).

The diastereoisomer ratio (α/β) was calculated by integration of the ^1H and ^{13}C NMR data from the crude reduction residue. Separation of diastereoisomers **4α** and **4β** was carried out by fractional crystallization or stirring with hexane (see Experimental Section).

The configurational assignment of **4** was ascertained by ^1H NMR spectra of the isolated isomers.[16] For instance,

(1) Tramontini, M. *Synthesis* **1982**, 605–644.
(2) (a) Pohland, A.; Sullivan, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 4458. (b) *Ibid.* **1955**, *77*, 3400.
(3) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601.
(4) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.
(5) Moroni, P.; Cazaux, L.; Tisnes, P.; Zambeti, M. *Bull. Soc. Chim. Fr.* **1980**, 179.
(6) Perold, G. W.; von Rieche, F. V. R. *J. Am. Chem. Soc.* **1957**, *79*, 465.
(7) Drefahl, G.; Hörhold, H. H. *Chem. Ber.* **1964**, *97*, 159.
(8) (a) Jäger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133. (b) Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101. (c) Jäger, V.; Buss, V.; Schwab, W. *Ibid.* **1980**, 122.
(9) Lora Tamayo, M.; Madroñero, R.; García Muñoz, G.; Leipprand, H. *Chem. Ber.* **1964**, *97*, 2234.
(10) Samaddar, A. K.; Konar, S. K.; Nasipuri, D. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1449.
(11) Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall Inc.: Engelwood Cliffs, NJ, 1971; pp 103–108.
(12) (a) Lyapova, M. J.; Kurtev, B. J. *Chem. Ber.* **1969**, *102*, 3739. (b) *Ibid.* **1971**, *104*, 131. (c) Lyapova, M. J.; Kurtev, B. J.; Pojarlieff, I. G. *J. Chem. Res. (S)* **1983**, 62–63.
(13) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255.
(14) Hoberg, H.; Barluenga, J. *Synthesis* **1970**, 142.
(15) For the reactivity of these systems see: (a) Barluenga, J.; Tomás, M.; López Ortiz, J.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1891. (b) Barluenga, J.; Jardón, J.; Rubio, V.; Gotor, V. *J. Org. Chem.* **1983**, *48*, 1379 and references cited therein.

(16) The characterization of the isomer **4β** of compounds **4a–g** was made by studying the spectral data from a β isomer enriched mixture.

0022-3263/85/1950-4052$01.50/0

Table II. γ-Amino Alcohols 4 Obtained by Reduction of 2 and 3

4[a]	R^4	R^6	α/β[b]	yield, %	mp, °C α	mp, °C β
a	C_6H_5	H	85/15 (88/12)[h] (65/35)[o]	85 (85)[h] (83)[o]	99–100	c
b	p-$CH_3C_6H_4$	H	87/13 (95/5)[d] (74/26)[i] (96/4)[m] (55/45)[o]	88 (87)[d] (91)[i] (88)[m] (89)[o]	106–107	c
c	p-ClC_6H_4	H	88/12 (65/35)[o]	89 (82)[o]	121–123	c
d	C_6H_5	CH_2CH_3	77/23 (85/15)[e] (78/22)[h] (60/40)[i] (72/28)[j] (74/26)[k] (74/26)[l]	83 (80)[e] (81)[h] (83)[i] (85)[j] (80)[k] (79)[l]	87–89	c
e	p-$CH_3C_6H_4$	CH_2CH_3	74/26	96	95–97	c
f	C_6H_5	$CH_2CH(CH_3)_2$	79/21	100	92–94	c
g	C_6H_5	$CH_2C_6H_{11}$	78/22	88	100–102	c
h	C_6H_5	CH_3	61/39 (65/35)[f]	85 (85)[f]	103–105	98–100
i	p-$CH_3C_6H_4$	CH_3	63/37	88	105–107	89–90
j	C_6H_5	$CH_2C_6H_5$	40/60 (49/51)[g] (25/75)[i] (37/63)[l] (44/56)[n]	93 (88)[g] (90)[i] (90)[l] (94)[n]	135–137	oil
k	p-$CH_3C_6H_4$	$CH_2C_6H_5$	38/62	92	134–136	oil
l	C_6H_5	$CH_2C_6H_4CH_3$-p	44/56	90	123–125	oil
m	C_6H_5	$CH_2C_6H_4Cl$-p	50/50	97	87–89	oil

[a] $R^1 = C_6H_5$, $R^3 = CH_3$. [b] By ^1H and ^{13}C NMR of the crude residue (estimated error ≤ ±2), Method A ($LiAlH_4$/THF). [c] Not isolated (see Experimental Section). [d] Method A ($LiAlH_4$/**2b** ratio 1/1). [e] Method A ($LiAlH_4$/**3a** ratio 1.3/1). [f] Method A ($LiAlH_4$/**3e** ratio 1.5/1). [g] Method A ($LiAlH_4$/**3g** ratio 1.3/1). [h] Method A ($LiAlH_4$/ether). [i] Method B ($LiAlH_4$/THF at −70 °C). [j] Method C ($LiAlH_4$/THF, $Ti(OEt)_4$ was utilized). [k] Method C ($LiAlH_4$/THF, $TiCl_4$ was utilized). [l] Method C ($LiAlH_4$/THF, $B(OEt)_3$ was utilized). [m] Method C (**2b**/$TiCl_4$/$LiAlH_4$ ratio 1/1.2/1.5). [n] Method C (**3g**/$B(OEt)_3$/$LiAlH_4$ ratio 1/1.2/1.5). [o] Method D (Na/*i*-PrOH).

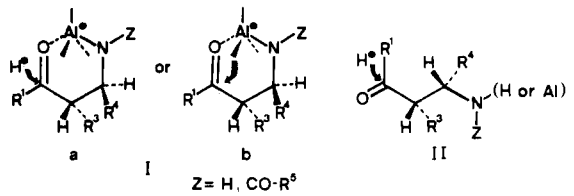
the ^1H NMR spectrum of **4hα** shows two characteristic doublets centered at δ 4.90 (1 H, J = 3.0 Hz) and 3.35 (1 H, J = 7.5 Hz), while that of **4hβ** shows two characteristic doublets centered at δ 4.55 (1 H, J = 9.0 Hz) and 3.40 (1 H, J = 10.5 Hz). In both cases this corresponds to the H in R^1–CH< and R^4–CH< groupings, respectively.[17] These data together with the tendency of these systems to form rings set by hydrogen bonds[18] show us that the prevailing conformations for the isomers **4α** and **4β** are those shown below.

4α **4β**

The experimental results (see Table II) indicate that the reaction takes place with high stereoselectivity for the amino derivatives (R^6 = H, entries **4a–c**)[19] and decreases for *N*-acyl derivatives (entries **4d–m**) in the sense R^5 = alk > OR > Ar. These results contrast with those obtained by Lyapova and co-workers.[12] This author concludes that the reduction of systems like **2** and **3** (R^3 = Ph) with $LiAlH_4$ gives, independent of the nature of R^5, only γ-amino alcohols α. However, this difference can be explained by taking into account the influence that the nature of R^3 has on the selectivity of the reaction. It is known that the stereoselectivity increases with the increasing steric requirements, in the sequence $R^3 = CH_3 < CH_2Ph < Ph$.[20]

Although the change of solvent from THF to ether does not lead to appreciable variations in the selectivity, the temperature and the amount of hydride do influence on the diastereoisomer ratio. A lowering in the temperature increases the relative amount of β in all investigated cases (see Table II). When a very little excess of $LiAlH_4$ was used, an increase in α was noted (see Table II).

These facts can be interpreted by supposing that the reaction takes place through the joint participation of two models,[1] namely, a rigid cyclic model (I) (a or b), which leads principally to the α isomer, and an open chain model (II), which gives fundamentaly the β isomer. They would necessarilly be formed by complexation of AlH_3^- at NHZ (Z = H, COR^5) and subsequent attack of one hydride to the less hindered face of a carbonyl group.



a b I II

Z= H, CO-R^5

The variation in the observed stereoselectivity for amino and *N*-acyl derivatives **2** and **3** can be based on the extent of participation of each of the models in the transition state.[21] Experimental results (see Table II) suggest that the cyclic model I is the predominant one for amino derivatives, whereas increased participation of model II is observed for *N*-acyl derivatives. Significantly, lower temperature enhances the participation of model II.

These results prompted us to attempt improving the stereoselectivity by ensuring a rigid cyclic transition state. So, the reactions were run in the presence of chelating agents such as $TiCl_4$, $Ti(OEt)_4$, and $B(OEt)_3$;[22,23] however, no great variations of selectivity (less than 6%) were obtained.

II. Cyclic Derivatives of 4. Configurational Assignment. The configurational assignment made for γ-amino alcohols **4** can be definitely and complementary ratified by studying the stereochemistry of their cyclic derivatives 2-oxotetrahydro-1,3-oxazines **5** and tetrahydro-1,3-oxazines **8**. Compounds **5** and **8** have been widely studied in the last few years due to their biological activity.[24]

(17) The ^1H NMR spectrum of **D-4a** (see Experimental Section) corroborates the relative positions assigned to the H in R^1–CH(D)< and R^4–CH< groupings for the γ-amino alcohols **4**.

(18) See ref 3, 4, 8, 11, and 12.

(19) The reduction of **2** with the less selective Na/*i*-PrOH leads to an approximate diastereoisomer ratio: α/β = 60/40 for compounds **4a–c** (see Table II).

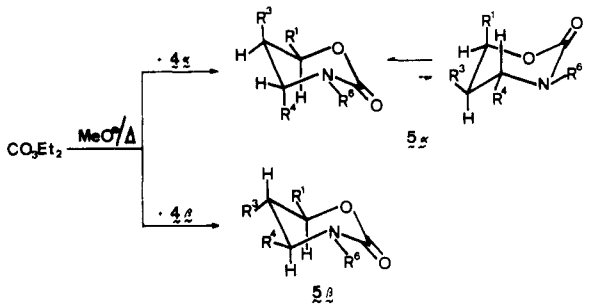
(20) Angiolini, L.; Tramontini, M. *J. Org. Chem.* **1974**, *39*, 2056.

(21) The reason for this would be the different complexing abilities of the substrate and the solvent for lithium aluminum hydride (see ref 1, p 612).

(22) Reetz, M. T. *Angew. Chem.* **1984**, *96*, 542.

(23) Maier, G.; Schmitt, R. K.; Seipp, U. *Chem. Ber.* **1985**, *118*, 722 and references cited therein.

Scheme III



Scheme IV

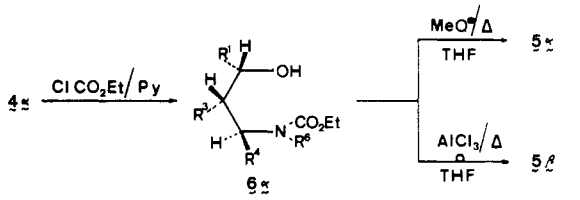


Table III. 2-Oxotetrahydro-1,3-oxazines 5 Obtained by Reaction of 4 with CO_3Et_2 or $ClCO_2Et$

no.[a]	R^4	R^6	yield, %	mp, °C
5aβ	C_6H_5	H	90[b]	256–257
5bα	*p*-$CH_3C_6H_4$	H	85[c] (89)[d]	155–157
5bβ	*p*-$CH_3C_6H_4$	H	91[b]	232–233
5cα	C_6H_5	CH_3	89[c]	104–106
5dβ	C_6H_5	$CH_2C_6H_5$	88[c]	196–198

[a] $R^1 = C_6H_5$, $R^3 = CH_3$. [b] Obtained from the reaction of **6α** with $AlCl_3$. [c] Method A (reaction of **4** with CO_3Et_2/MeO^-Na^+). [d] Method B (reaction of **6α** with MeO^-Na^+).

The most general preparative method of **5** is the reaction of **4** with carbonic acid difunctionalized derivatives.[4,8,12,24] Reaction of **4** (α or β) with an excess of diethyl carbonate in the presence of MeO^-Na^+ at 100 °C for several hours leads to the corresponding cyclic derivatives **5** (α and β, respectively) in nearly quantitative yields (Scheme III and Table III).

The study of ^1H NMR spectra of compounds **5** shows that the diaxial–equatorial conformation is the prevailing one for the α isomer and that the more stable triequatorial conformation is the prefered one for the β isomer. For instance, the ^1H NMR spectrum of compound **5bα** displays two doublets centered at 4.30 (1 H, J = 3.0 Hz) and 5.25 (1 H, J = 3.0 Hz) while the ^1H NMR spectrum of compound **5bβ** displays two doublets centered at 4.20 (1 H, J = 9.5 Hz) and 4.90 (1 H, J = 9.5 Hz) corresponding, in both cases, to the H in the R^4–CH< and R^1–CH< groupings respectively. The values of δ, the multiplicity of the signals, and the values of the coupling constants corroborate the proposed stereochemistry.

The reaction of **4α** with $ClCO_2Et$/Py gives the *N*-carbethoxy substituted open chain derivatives **6α** which by treatment with MeO^-Na^+ afford the corresponding cyclic derivatives (e.g., **6α** → **5α**), with retention of the stereochemistry. However if the cyclization of **6α** is carried out with $AlCl_3$,[25] surprisingly only compound **5β** is obtained in nearly quantitative yields. In other words, the reaction has taken place with inversion of the configuration in C-1 of starting γ-amino alcohol **4α** (see Scheme IV and Tables III and IV).

(24) (a) Eckstein, Z.; Urbański, T. *Adv. Heterocycl. Chem.* **1963**, *2*, 311–342. (b) *Ibid.* **1978**, *23*, 1–53. (c) Kato, T.; Katagiri, N.; Kamamoto, Y. *Heterocycles* **1980**, *14*, 1333–1403.

(25) Barluenga, J.; Muñiz, L.; Iglesias, M. J.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1*, 1984, 611.

Table IV. *N*-Carbethoxy Derivatives 6 Obtained by Reaction of 4 with $ClCO_2Et$ in Pyridine

no.[a]	R^4	yield, %	mp, °C
6aα	C_6H_5	99	137–139
6bα	*p*-$CH_3C_6H_4$	95	137–139

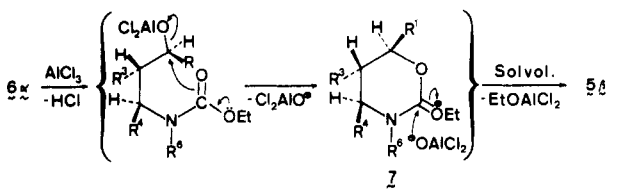
[a] $R^1 = C_6H_5$, $R^3 = CH_3$, $R^6 = H$.

Table V. Tetrahydro-1,3-oxazines 8 Obtained by Reaction of 4 with H_2CO

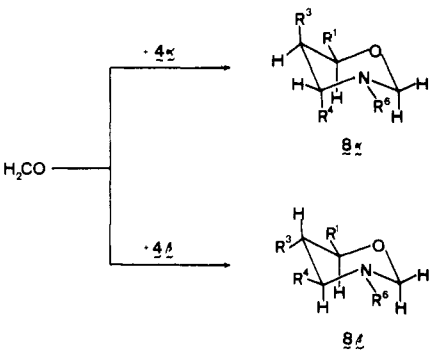
no.[a]	R^4	R^6	yield, %	mp, °C
8aα	C_6H_5	H	83	oil
8bα	C_6H_5	$CH_2C_6H_5$	80	oil
8bβ	C_6H_5	$CH_2C_6H_5$	91	87–89

[a] $R^1 = C_6H_5$, $R^3 = CH_3$.

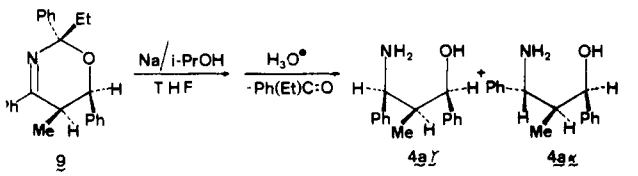
Scheme V



Scheme VI



Scheme VII



The isomerization can be reasonably explained in terms of nucleophilic attack of the carbonilic oxygen atom from the carbethoxy group to the carbinolic carbon as indicated in Scheme V. The final solvolysis would then lead, via **7**, to compound **5β**.

It is noteworthy that independent of the solvent used in the final solvolysis (H_2O/OH^-, MeOH or NEt_3) only the cyclic derivative **5β** is obtained. This, corroborates the proposed mechanism.

Reduction of **5** (α or β) with $LiAlH_4$ in THF yields the previously obtained γ-amino alcohols **4** (α or β, respectively).

Tetrahydro-1,3-oxazines **8** are obtained by reaction of **4** with formaldehyde. This process runs, as it was expected, with retention of the stereochemistry of the starting γ-amino alcohol (Scheme VI, Table V). The values of coupling constants from the ^1H NMR spectra of compounds **8** (see Experimental Section) confirm the proposed stereochemistry.

To complement and corroborate the structure of **4** by an alternative method we have carried out an independent synthesis of these compounds. For instance, compound

4α can be obtained by a sequence that includes reduction of the 5,6-dihydro-1,3-oxazine 9[26] with Na/*i*-PrOH followed by an acid hydrolysis and a subsequent separation and purification of the resulting mixture of diastereoisomers (4a, Scheme VII).

Conclusions

The $LiAlH_4$ reduction of β-amino ketones 2 and *N*-acyl derivatives 3 affords γ-amino alcohols 4 with three chiral centers in a highly stereoselective synthesis which is a more general and more simple method than those so far described in the literature. The stereoselectivity largely depends on the nature of the starting substrate as well as on the temperature and on the number of hydride equivalents.

The assignment of the relative stereochemistry of γ-amino alcohols 4 is verified by spectroscopic study of their cyclic derivatives, 2-oxotetrahydro-1,3-oxazines 5 and tetrahydro-1,3-oxazines 8.

Finally, the sequence 4α → 6α → 5β → 4β constitutes an excellent preparative procedure of the β isomers, generally obtained as the minor isomer in the synthesis of 4.

Experimental Section

General Methods. Melting points are uncorrected. Infrared spectra were recorded in a Nujol or KBr mixture on a Pye Unicam SP-1000 spectrophotometer. The ^1H NMR spectra were determined on a Varian FT-80A spectrometer with internal tetramethylsilane as the reference. The ^{13}C NMR spectra were determined on a Varian FT-80A set for performing "off-resonance". Mass spectra were taken on a Hewlett-Packard 5930A spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240.

Materials. β-Amino ketones 2 and β-acylamino ketones 3 used as starting materials were prepared according to literature methods.[13] The spectral data for compounds 2 and 3 that have not been described previously are included in the Supplementary Material. Tetrahydrofuran was distilled from sodium benzophenone under argon prior to use. All the other reagents were commercially available and were used as received.

General Preparative Procedure of γ-Amino Alcohols 4. Method A. Reduction of 2 and 3 with $LiAlH_4$. A solution of 2[27] or 3 (10 mmol) in anhydrous THF was slowly added to an ice-cooled stirred slurry of lithium aluminum hydride (1.5 g, 40 mmol) in anhydrous THF (30 mL) under argon. Evolution of hydrogen was observed during the addition. The mixture was refluxed[28] for 15 h and then treated with anhydrous MeOH (15 mL) diluted in THF (20 mL). When the evolution of gas was complete, water was added and the mixture extracted with ether; the organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. γ-Amino alcohols 4 were obtained as a mixture of diastereoisomers. Reaction yields and diastereoisomer ratios are listed in Table II.

Separation of Diastereoisomers of 4a–g. The crude product containing the two isomers was dissolved in hot *n*-hexane–chloroform (6:1). From the solution, isomer 4α was isolated by crystallization and filtered. From the filtrate, solvent was removed and several treatments with hexane lead us to a β isomer enriched mixture. Melting points for isomer 4α are shown in Table II.

Separation of Diastereoisomers of 4h–i. The crude product containing the two isomers was dissolved in hot *n*-hexane–chloroform (6:1). From the solution, isomer 4α was the first isolated by crystallization. Isomer 4β could be isolated after consecutive crystallizations. Melting points are given in Table II.

Separation of Diastereoisomers of 4j–m. The crude product containing the two isomers was suspended in hexane (20 mL) with stirring. The slurry was filtered. The hexane-insoluble solid, 4α, was recrystallized from *n*-hexane–chloroform (6:1). From the filtrate, hexane was removed and isomer 4β was distilled from the residue. Melting points for isomer 4α are given in Table II.

Method B. Low Temperature Reduction of 2 and 3 with $LiAlH_4$. A solution of 2[27] or 3 (10 mmol) in anhydrous THF was slowly added to a −70 °C cooled stirred slurry of lithium aluminum hydride (1.5 g, 40 mmol) in anhydrous THF (30 mL) under argon. Evolution of hydrogen was also observed during the addition. The mixture was stirred at −70 °C for 7 h and then refluxed for 15 h. The subsequent operations were the same as those from Method A. γ-Amino alcohols 4 were obtained as a mixture of diastereoisomers. Reaction yields and diastereoisomer ratios are shown in Table II.

Method C. Reduction of 2 and 3 with $LiAlH_4$ in the Presence of a Chelating Agent. To an ice-cooled solution of 2 or 3 (10 mmol) in anhydrous THF was added a chelating agent (12 mmol, see Table II). The mixture was kept in the ice bath and stirred for $^1/_2$ h and then $LiAlH_4$ (40 mmol) was added. The subsequent operations were the same as those from Method A. γ-Amino alcohols 4 were obtained. Reaction yields and diastereoisomer ratios are given in Table II.

Method D. Reduction of 2 with Na/*i*-PrOH. A solution of 2 (10 mmol) in anhydrous THF (30 mL) and anhydrous *i*-PrOH (16 mL) was added dropwise to a mixture of Na (2.3 g, 100 mmol) and anhydrous THF (20 mL) at room temperature. When the addition was complete, the solution was stirred at room temperature until totally discolored (4 h). The solution was then hydrolyzed with 200 mL of water and extracted with ether. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. γ-Amino alcohols 4 were obtained as a mixture of diastereoisomers. Reaction yields and diastereoisomer ratios are shown in Table II.

3-Amino-2,*N*-dimethyl-1,3-diphenyl-1-propanol (4h). Method A: 4h (85%) was obtained by reaction of 3e with $LiAlH_4$.

***(S,R,S/R,S,R)*-4hα**: IR (KBr) 3320, 3280, 1620, 780, 770, 720 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.50 (d, 3 H, J = 7.5 Hz), 2.20 (m, 1 H), 2.20 (s, 3 H), 3.35 (d, 1 H, J = 7.5 Hz), 4.90 (d, 1 H, J = 3.0 Hz), 7.00–7.50 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 142.52, 141.32, 126.30–128.04, 76.25, 67.33, 43.71, 33.51, 13.96; MS, m/e 255 (M^+) 224, 148, 120, 42.

Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 79.89; H, 8.20; N, 5.53.

***(R,R,S/S,S,R)*-4hβ**: IR (KBr) 3300, 1620, 780, 730, 720 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.25 (d, 3 H, J = 7.5 Hz), 2.20 (m, 1 H), 2.20 (s, 3 H), 3.40 (d, 1 H, J = 10.5 Hz), 4.55 (d, 1 H, J = 9.0 Hz), 4.85 (br s, NH and/or OH), 7.00–7.50 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 144.28, 141.65, 127.06–128.45, 81.99, 71.85, 44.11, 33.37, 15.15.

Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 80.01; H, 8.17; N, 5.50.

Spectral data for compounds 4a–m (and D–4a) are included as supplementary material.

Preparation of 5-Methyl-2-oxo-6-phenyl-4-*p*-tolyltetrahydro-1,3-oxazine ((*S,R,S/R,S,R*)-5bα). Method A.[8b] To a solution of 4bα (4 mmol) in diethyl carbonate (5 mL) were added anhydrous methanol (0.2 mL, 5 mmol) and sodium (10 mg, 0.5 mmol). The solution was heated at 100 °C for 15 h and then hydrolyzed with 3 N KOH and extracted with ether. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue, a white solid (85%), was purified by recrystallization from *n*-hexane–chloroform (6:1): mp 155–157 °C; IR (Nujol) 3280, 1710, 800, 770, 740, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.90 (d, 3 H, J = 7.5 Hz), 2.20 (m, 1 H), 2.30 (s, 3 H), 4.30 (m, 1 H) (+ D_2O, 4.30 (d, 1 H, J = 3.0 Hz)), 5.25 (d, 1 H, J = 3.0 Hz), 7.00–7.50 (m, 9 H); ^{13}C NMR ($DCCl_3$) δ 154.06, 138.35, 137.51, 137.11, 125.12–129.33, 77.38, 58.74, 38.64, 20.83, 12.77; MS, m/e 281 (M^+) 222, 132, 117, 91, 41.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.50; H, 6.45; N, 4.97.

Method B. To a solution of 6bα (4 mmol) in anhydrous THF (40 mL) was added anhydrous methanol (0.2 mL) followed by sodium (10 mg). The solution was refluxed for 15 h, then hydrolyzed with 3 N KOH, and extracted with ether. The extract

(26) Preparation and reactivity of these compounds is being studied in our laboratory. Barluenga, J.; Joglar, J.; Fustero, S.; Gotor, V., work in progress.

(27) 2·hydrochloride can be used instead of 2 following the same procedure. There is no difference in reaction yields and diastereoisomer ratios.

(28) Reduction of 2 (or 2·hydrochloride) can be carried out at room temperature with THF or ether. No change in reaction yields and diastereoisomer ratios is noted.

was dried over sodium sulfate and evaporated to give **5bα** as a white solid (89%).

Preparation of 5-Methyl-2-oxo-6-phenyl-4-*p*-tolyltetrahydro-1,3-oxazine ((*S*,*R*,*R*/*R*,*S*,*S*)-5bβ). To a solution of **6bα** (5 mmol) in anhydrous THF (30 mL) in an ice bath was added aluminum trichloride (0.8 g, 6 mmol) with stirring. The solution was refluxed for 15 h, then hydrolyzed with 3 N KOH, and extracted with ether. The extract was dried, filtered, and evaporated. The residue, a white solid (91%), was purified by recrystallization from *n*-hexane–chloroform (6:1): mp 232–233 °C; IR (Nujol) 3260, 1710, 820, 780, 770, 740 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.50 (d, 3 H, J = 7.5 Hz), 2.00 (m, 1 H), 2.30 (s, 3 H), 4.20 (d, 1 H, J = 9.5 Hz), 4.90 (d, 1 H, J = 9.5 Hz), 5.50 (br s, NH), 7.00–7.50 (m, 9 H); ^{13}C NMR ($DCCl_3$) δ 153.83, 138.47, 137.34, 136.55, 127.10–129.49, 84.54, 62.30, 40.55, 20.99, 12.82.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.91; H, 6.93; N, 4.53.

Preparation procedure and spectral data for compounds **5aβ**, **5cα**, and **5dβ** are included as supplementary material.

General Preparative Procedure of 1-(Carbethoxyamino)-3-propanols 6α.[8b] To a solution of **4α** (10 mmol) in anhydrous THF (40 mL) and anhydrous pyridine (5 mL) in a ice bath was added ethyl chloroformate (1.2 mL, 12 mmol) with stirring. The mixture was refluxed for 10 h, then poured onto 3 N KOH, and extracted with ether. The extract was dried over sodium sulfate and evaporated under reduced pressure. The residual 1-(carbethoxyamino)-3-propanols **6α** were purified by recrystallization from *n*-hexane–chloroform (6:1). Reaction yields and melting points are shown in Table IV.

1-(Carbethoxyamino)-2-methyl-1,3-diphenyl-3-propanol ((*S*,*R*,*S*/*R*,*S*,*R*)-6aα). Obtained from the reaction of **4aα** and ethyl chloroformate: IR (Nujol) 3400, 1700, 760, 740, 710 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.60 (d, 3 H), 1.15 (t, 3 H), 2.00 (m, 1 H), 3.40 (br s, OH) 4.00 (q, 2 H), 4.70 (m, 1 H), 4.90 (br s, NH), 5.70 (d, 1 H), 7.00–7.40 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 157.10, 143.32, 140.90, 125.32–128.53, 71.85, 60.94, 59.16, 45.30, 14.39, 10.05.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.35; N, 4.47. Found: C, 72.67; H, 7.51; N, 4.53.

Spectral data for compound **6bα** are included as supplementary material.

Reduction of 5 with $LiAlH_4$. Reduction of **5** with $LiAlH_4$ was carried out by following the procedure described for the preparation of **4** (Method A).

Reduction of 5-Methyl-2-oxo-6-phenyl-4-*p*-tolyltetrahydro-1,3-oxazine ((*S*,*R*,*S*/*R*,*S*,*R*)-5bα). Compound **4iα** (80%) was obtained.

Results from the reduction of **5aβ** and **5bβ** are included as supplementary material.

General Preparative Procedure of Tetrahydro-1,3-oxazines 8.[24] To a solution of **4** (5 mmol) in ether at room temperature was added 35–40% aqueous formaldehyde (5 mmol). The solution was stirred for 16 h at room temperature. Solvent was removed and the residue dried under reduced pressure to yield tetrahydro-1,3-oxazines **8**. Reaction yields are given in Table V.

5-Methyl-4,6-diphenyltetrahydro-1,3-oxazine ((*S*,*R*,*S*/*R*,*S*,*R*)-8aα) was obtained from the reaction of **4aα** and formaldehyde. The residue was purified by distillation: IR (film) 3360, 1600, 750, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.90 (d, 3 H, J = 7.5 Hz), 2.45 (m, 1 H), 2.80 (br s, NH), 4.00 (d, 1 H, J = 3.0 Hz), 4.45 (d, 1 H, J = 12.0 Hz), 4.65 (d, 1 H, J = 12.0 Hz), 4.70 (d, 1 H, J = 3.0 Hz), 7.00–7.70 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 141.70 141.07, 125.10–128.36, 76.21, 75.64, 58.61, 36.22, 12.83; MS, m/e 253 (M^+), 223, 209, 180, 134, 118.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.51; N. 5.53. Found: C, 80,57; H, 7.64; N, 5.67.

Spectral data for compounds **8bα** and **8bβ** are included as supplementary material.

Reduction Followed by Hydrolysis of 2-Ethyl-5-methyl-2,4,6-triphenyl-5,6-dihydro-1,3-oxazine (9). Reduction of **9** with Na/*i*-PrOH was carried out by following the procedure described for preparation of **4** (Method C). A yellow oil was obtained. The oil was solved in THF. 4 N HCl was added to the solution and the mixture heated for 7 h, treated with 3 N KOH until basic, and extracted with ether. The organic layer was dried, filtered, and evaporated. γ-Amino alcohol **4a** (81 %) was obtained as a mixture of diastereoisomers.

Separation of the Diastereoisomers of 4a. The crude product containing two isomers (γ/α = 66/34, calculated by ^1H and ^{13}C NMR) was suspended in hexane and stirred. The slurry was filtered. The hexane-insoluble solid was identified as **4aα**. From the filtrate hexane was removed and isomer **4aγ** was distilled.

(*S*,*R*,*R*/*R*,*S*,*S*)-4aγ: IR (film) 3300, 1600, 740, 700 cm^{-1}; ^1H NMR ($DCCl_3$) δ 0.70 (d, 3 H, J = 7.5 Hz), 2.10 (m, 1 H), 3.25 (br s, NH and/or OH), 4.35 (d, 1 H, J = 3.0 Hz), 5.20 (d, 1 H, J = 3.0 Hz), 7.00–7.50 (m, 10 H); ^{13}C NMR ($DCCl_3$) δ 144.71, 143.56, 125.42–128.42, 77.25, 59.53, 45.48, 12.10.

Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.87; H, 7.93; N, 5.60.

Registry No. **2a**, 85356-29-2; **2b**, 85356-31-6; **2c**, 97293-65-7; **3a**, 85356-36-1; **3b**, 85356-37-2; **3c**, 97210-88-3; **3d**, 97210-89-4; **3e**, 97210-90-7; **3f**, 97210-91-8; **3g**, 97210-92-9; **3h**, 97210-93-0; **3i**, 97210-94-1; **3j**, 97210-95-2; **4aα**, 97210-96-3; **4aβ**, 97275-75-7; **4bα**, 97210-97-4; **4bβ**, 97275-76-8; **4cα**, 97210-98-5; **4cβ**, 97275-77-9; **4dα**, 97210-99-6; **4dβ**, 97275-78-0; **4eα**, 97211-00-2; **4eβ**, 97275-79-1; **4fα**, 97211-01-3; **4fβ**, 97275-80-4; **4gα**, 97211-02-4; **4gβ**, 97275-81-5; **4hα**, 97211-03-5; **4hβ**, 97275-82-6; **4iα**, 97211-04-6; **4iβ**, 97275-83-7; **4jα**, 97211-05-7; **4jβ**, 97275-84-8; **4kα**, 97211-06-8; **4kβ**, 97275-85-9; **4lα**, 97211-07-9; **4lβ**, 97275-86-0; **4mα**, 97211-08-0; **4mβ**, 97275-87-1; **5aβ**, 97211-09-1; **5bα**, 97211-10-4; **5bβ**, 97275-88-2; **5cα**, 97234-62-3; **5dβ**, 97211-11-5; **6aα**, 97211-12-6; **6bα**, 97211-13-7; **8aα**, 97211-14-8; **8bα**, 97211-15-9; **8bβ**, 97275-89-3; **9**, 97211-16-0; CH_3COCl, 75-36-5; $ClCOCH(CH_3)_2$, 79-30-1; $ClCOC_6H_{11}$, 2719-27-9; $ClCO_2Et$, 541-41-3; PhCOCl, 98-88-4; *p*-$CH_3C_6H_4COCl$, 874-60-2; *p*-ClC_6Ch_4COCl, 122-01-0; $Ti(OEt)_4$, 3087-36-3; $B(OEt)_3$, 150-46-9; $TiCl_4$, 7550-45-0; formaldehyde, 50-00-0.

Supplementary Material Available: Spectral and analytical data for compounds **2c**, **3c–j**, **4a–m**, **5aβ**, **5cα**, **5dβ**, **6aα**, **6bα**, **8aα**, **8bα**, **8bβ** (18 pages). Ordering information is given on any current masthead page.

Quassinoids. An Approach to the BCDE Rings of Bruceantin

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Synthesis of a model **28** for the BCDE rings of bruceantin via a BC → BCE → BCED ring strategy is presented. The sequence includes Diels–Alder reaction of methyl 3,5-hexadienoate **9** and quinone **8** derived from *o*-vanillyl alcohol, selenocyclization of hydroxy diester **22**, and lactone formation to give the BCDE system **25**. Manipulation on **25** showed the viability of its functional groups for further development in the synthetic strategy.

The quassinoids constitute a large and constantly expanding family of terpenoid bitter principles found in *Simaroubaceae*, a large botanical family of pantropical distribution.[2] Quassin (**1**) was isolated in 1973[3] and its

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