X-ray Crystallographic Study of Substituted Perhydropyrimidinones. Extreme Changes in Ring Conformation

Yara Ramírez-Quirós,[1] Margarita Balderas,[1] Jaime Escalante,[1] Delia Quintana,[1] Itzell Gallardo,[1] Domingo Madrigal,[1] Elies Molins,[2] and Eusebio Juaristi*[,1,3]

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, 07000 México, DF, Mexico, and Institut de Ciència de Materials de Barcelona (CSIC), Campus Universitat Autònoma de Barcelona, 08193 Cerdanyola, Spain

Received August 16, 1999

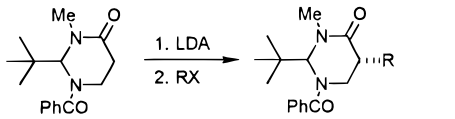
X-ray crystal structures of 20 differently substituted perhydropyrimidin-4-ones are presented. Analysis of these data reveal a remarkable conformational sensitivity of a six-membered ring to substitution. Thus half-chair, envelope, boat, twist-boat, and intermediate conformations are found for the six-membered heterocycle, providing evidence for a relatively flat conformational energy surface in this ring. Interpretation of the preferred conformations is advanced in terms of steric interactions among substituents and, in some cases, as the result of particular conformational ($A^{1,3}$ strain, anomeric) effects.

Introduction

One of the basic tenets of conformational analysis establishes that substituents in six-membered rings are most stable in equatorial rather than axial orientations.[4] Nevertheless, a well-recognized exception pertains to the anomeric effect, which has attracted considerable experimental and theoretical attention.[5] A second tenet in conformational analysis is that staggered conformers are significantly more stable than eclipsed ones, to the extent that the latter are usually disregarded.[4] However, structural data accumulated in the past decade have provided experimental confirmation of the existence of nonstaggered, stable eclipsed conformation in several saturated compounds.[6,7]

Some years ago, 1-benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (*rac*-**1**) was alkylated with high diastereoselectivity via the corresponding enolate.[8] (Scheme 1). X-ray crystal-structure determinations used to elucidate the stereochemical outcome of this reaction revealed[9] an axial disposition of the *tert*-butyl group at C(2) (consequence of a powerful $A^{1,3}$ effect[10]), which directs electrophilic addition toward the enolate face opposite to this group.

Scheme 1



rac-**1** (high *trans* diastereoselectivity)

Subsequent X-ray crystallographic structure determinations of differently substituted perhydropyrimidinones, to be described in the present paper, disclosed yet another "anomaly" to general tendencies in the conformational behavior of six-membered rings:[11] it is usually observed that conformational energy surfaces for a particular ring system exhibit pronounced energy minima at specific conformational coordinates.[11b] However, we have gathered structural data indicating that relatively subtle changes in substitution patterns for perhydropyrimidin-

* Corresponding author.
(1) Instituto Politécnico Nacional.
(2) Institut de Ciència de Materials.
(3) E-mail: juaristi@relaq.mx.

(4) See, for example: (a) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(5) Recent monographs: (a) Thatcher, G. R. J., Ed. *The Anomeric Effect and Associated Stereoelectronic Effects*; ACS Symposium Series No. 539; American Chemical Society: Washington, DC, 1993. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995.

(6) Review: Juaristi, E. Stable Eclipsed Conformations. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; Wiley: New York, 1998; Vol. 4, pp 2688−2692.

(7) Leading original references: (a) Juaristi, E.; Martínez, R.; Méndez, R. A.; Toscano, R. A.; Soriano-García, M.; Eliel, E. L.; Petsom, A.; Glass, R. S. *J. Org. Chem.* **1987**, *52*, 3806−3811. (b) Anderson, J. E.; Watson, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 1517−1518. (c) Gordillo, B.; Juaristi, E.; Martínez, R.; Toscano, R. A.; White, P. S.; Eliel, E. L. *J. Am. Chem. Soc.* **1992**, *114*, 2157−2162. (d) Anderson, J. E.; Ijeh, A. I.; Storch, C.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1998**, *63*, 3310−3317.

(8) (a) Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553−2557. For applications in enantioselective synthesis, with enantiopure analogues: (b) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233−2246. (c) Juaristi, E.; Balderas, M.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3881−3888. (d) Juaristi, E.; Seebach, D. Enantioselective Synthesis of α-Substituted and α,β-Disubstituted β-Amino Acids via Chiral Derivatives of 3-Aminopropionic Acid. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; Chapter 13, pp 261−277.

(9) (a) Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradón, B.; Hidber, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mouriño, A.; Pfammatter, E.; Plattner, D. A.; Schickli, C.; Schweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913−934. (b) Murer, P.; Rheiner, B.; Juaristi, E.; Seebach, D. *Heterocycles* **1994**, *39*, 319−344. (c) See, also: Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335−360.

(10) Reviews: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. For a computational study, see: (c) Broeker, J. L.; Hoffmann, R. W., Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006−5017.

(11) (a) Juaristi, E., Ed. *Conformational Behavior of Six-Membered Rings. Analysis, Dynamics, and Stereoelectronic Effects*; VCH Publishers: New York, 1995. (b) Cremer, D.; Szabo, K. J. Ab Initio Studies of Six-Membered Rings: Present Status and Future Developments. In ref 11a, Chapter 3, pp 59−135.

10.1021/jo991297q CCC: $18.00
Published on Web 11/12/1999

4-ones produce drastic variations in the preferred conformation of the ring.

Results and Discussion

Although qualitative description of ring shapes is based on more or less intuitive comparison with some reference conformations such as chair, boat, or half-boat,[4] methods are available for the description of the conformations of cyclic molecules in quantitative terms.[12−14] The most successful procedure was worked out in 1975 by Cremer and Pople (CP),[11b,13] who made possible a general definition of ring puckering coordinates for the proper description of ring shape. According to the CP method, for a six-membered ring, the set of 3 puckering coordinates (amplitudes and phase angles deduced from the deviations z_j of the ring atoms from the "mean" plane) leads to the description of all possible conformations, in terms of total puckering Q, polar angle θ and phase angle ϕ. This method generally works very well, although it has been argued[14] that it sometimes fails in the description of ring conformations due to the dependence of the CP puckering parameters on the geometrical characteristics of the ring.

More recently, Zefirov, Palyulin, and Dashevskaya (ZPD) have proposed some modifications to the CP method, with the use of the endocyclic torsional angles ψ_j as a basic parameter for the calculation procedure. That is, instead of the normal deviations z_j from the mean plane, the values of $\sin(\psi_j/2)$ were used for determination of the puckering amplitudes and phase angles. There is some concern that the formulas advanced to compute relationships between puckering parameters (defined by the *z*-coordinates) and the endocyclic torsional angles (depending on both *x*-, *y*-, and *z*-coordinates) may not work well for large puckering and larger rings. Nevertheless, examination of this point can be made by comparison of the torsional angles that are recomputed from the calculated puckering parameters with the original torsional angles. If differences between the original and the recomputed values (σ) do not exceed 3−5°, then it is generally concluded that the ZPD method properly describes the conformation of the cyclic molecule under study. For the systems described in this paper, σ values were found not to exceed 1.5°.

Both in the CP and ZPD methods the calculated structural parameters allow schematic representation of the ring forms on the surface of a sphere where values of polar and phase angles dictate the distance between the point corresponding to the ring under study and the points of the extreme (canonical) conformations, such as chair, boat, or twist-boat, on the surface of the conformational sphere. (Figure 1).

The conformational analysis of 20 differently substituted 1-benzoylperhydropyrimidin-4-ones, **1**−**20** (Chart 1), was undertaken by means of the ZPD method and the CP method as implemented in the RICON[15] and RING96[16]

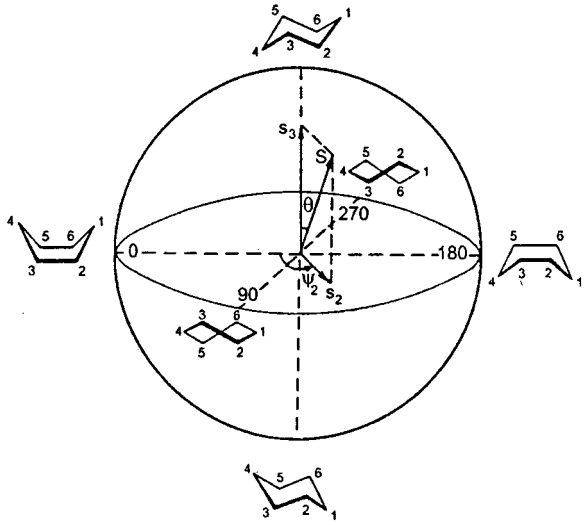


Figure 1. ZPD puckering parameters for the six-membered ring in the conformational sphere.[14] (Reproduced with permission of the Editor.)

computer programs, respectively, using the atomic coordinates derived from X-ray crystallographic analysis. For the purposes of this work, it was assumed that the crystal conformations of racemic pyrimidinones **3**, **7**, **8**, **15**, and **18**−**20** do not differ significantly from the structures of the same enantiopure compounds.[17]

Table 1 collects the conformational parameters for pyrimidinones **1**−**20** obtained by the ZPD method, and Table 2 collects the conformational parameters for the same compounds obtained by the CP method. Figures 2 and 3 present the distributions of these heterocycles in three-component triangle diagrams, which have been proposed as an alternative presentation of the spherical conformational map.[15] The most interesting feature revealed from these analyses is the extensive spread of ring structures over the different conformational extremes; this is, the pyrimidinone ring exhibits a remarkable sensitivity to the nature and position of the various alkyl or aryl substituents. This conclusion is reached both with the CP and ZPD methods. Comparison of data presented in Figures 2 and 3 reveals good agreement between the conformational distribution of the heterocyclic structures **1**−**20**, which is confirmed in the analysis summarized in Tables 1 and 2.

A fundamental characteristic of the perhydropyrimidinone ring is the presence of the endocyclic and exocyclic amide functions. Thus, most of the C(2)−N(1)−C(6) bond angles are between 115 and 120°, and the C(2)−N(3)−C(4) angles vary between 120 and 125°. As a consequence, the perhydropyrimidinones are rather flat molecules, which reduces the energy difference between extreme conformations (or, for that matter, any of the intermediate conformations).[18] Therefore, the perhydropyrimidinone ring is rather flexible, adjusting itself easily to the steric (and/or stereoelectronic; see below) requirements of the substituents.

In this context, the conformation of the perhydropyrimidinone ring is somewhat related to the conformation of the 4-cyclohexenone ring. Thus, it was of interest to compare the conformational behavior of heterocycles

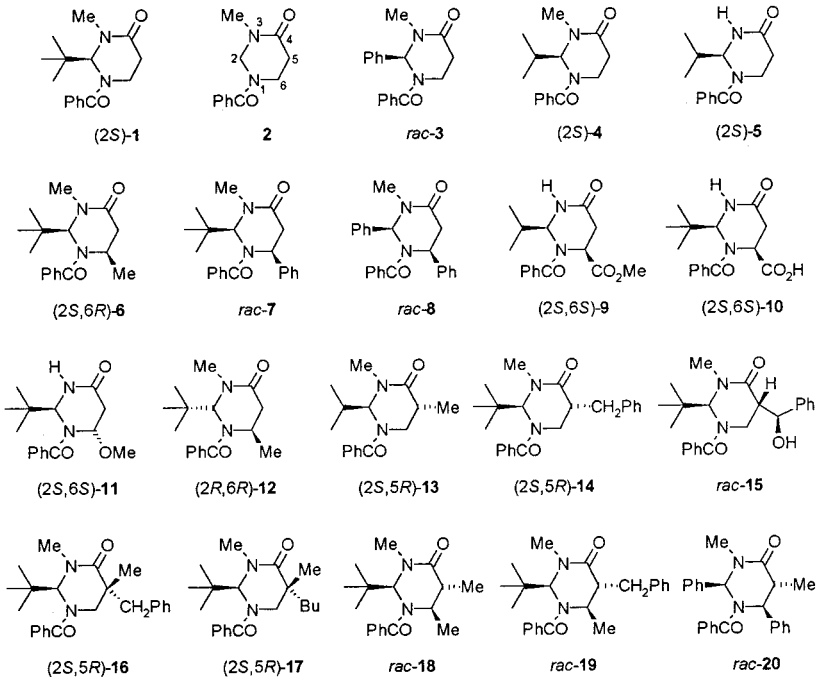
(12) For pioneering developments, especially with six-membered rings: (a) Kilpatrick, J. E.; Pitzer, K. S.; Spitzer, R. *J. Am. Chem. Soc.* **1947**, *69*, 2483−2488. (b) Dunitz, J. D. *Tetrahedron* **1972**, *28*, 5459−5467. (c) Buys, H. R.; Geise, H. J. *Tetrahedron Lett.* **1968**, 5619−5624. (d) Cano, F. H.; Foces-Foces, C.; García Blanco, S. *Tetrahedron* **1977**, *33*, 797−802. (e) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7047−7061.

(13) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354−1358.

(14) Zefirov, N. S.; Palyulin, V. A.; Dashevskaya, E. E. *J. Phys. Org. Chem.* **1990**, *3*, 147−158.

(15) Zotov, A. Y.; Palyulin, V. A.; Zefirov, N. S. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 766−773.

Chart 1[a]



[a] 1-Benzoylperhydropyrimidin-4-ones whose X-ray crystallographic structure and conformation are discussed in this paper.

Table 1. Conformational Parameters for Heterocycles 1−20, Calculated with the ZPD Method[a]

compd	S	S_2	S_3	θ	ψ	σ	conformation
(2*S*)-**1**	0.773	0.371	−0.678	28.7	8.6	0.60	between envelope and half-chair
2	0.823	0.398	−0.720	29.0	27.4	0.44	distorted half-chair
rac-**3**	0.806	0.395	−0.703	29.3	11.4	0.32	between envelope and half-chair
(2*S*)-**4**	0.702	0.595	−0.371	58.1	26.5	0.68	distorted screw-boat
(2*S*)-**5**	0.816	0.371	−0.727	27.1	22.0	0.61	between half-chair and envelope
(2*S*,6*R*)-**6**	0.654	0.649	−0.074	83.5	11.2	0.93	between boat and screw-boat
rac-**7**	0.730	0.727	0.065	84.9	16.8	1.31	between twist and boat
rac-**8**	0.766	0.764	−0.054	86.0	6.3	1.21	between boat and screw-boat
(2*S*,6*S*)-**9**	0.734	0.722	−0.130	79.8	6.8	1.09	between boat and screw-boat
(2*S*,6*S*)-**10**	0.578	0.569	−0.102	79.8	6.2	0.89	between boat and screw-boat
(2*S*,6*S*)-**11**	0.646	0.610	0.213	70.7	19.2	1.03	between envelope and twist
(2*R*,6*R*)-**12**	0.744	0.714	−0.208	73.8	24.2	1.46	between twist and envelope
(2*S*,5*R*)-**13**	0.771	0.759	−0.140	79.6	19.3	0.50	between twist and envelope
(2*S*,5*R*)-**14**	0.786	0.392	−0.682	29.9	7.2	0.62	between envelope and half-chair
rac-**15**	0.687	0.470	0.501	43.1	14.1	0.56	between envelope and screw-boat
(2*S*,5*R*)-**16**	0.758	0.449	−0.611	36.3	7.8	0.69	between envelope and half-chair
(2*S*,5*R*)-**17**	0.807	0.374	−0.715	27.6	17.3	0.99	between half-chair and envelope
rac-**18**	0.679	0.679	0.031	87.4	10.5	0.51	between boat and twist
rac-**19**	0.640	0.615	−0.175	74.2	18.4	0.87	between envelope and twist
rac-**20**	0.828	0.821	0.107	82.6	6.3	1.06	between boat and screw-boat

[a] S = total puckering amplitude, $S_2 = S \sin\theta$, $S_3 = S \cos\theta$, θ = polar angle, ψ = phase angle, σ = deviation of the calculated torsional angles from the initial values.

1−**20** with that exhibited by substituted 4-cyclohexenones. A search through the Cambridge Structural Database (CSD) afforded 72 crystallographic structures (R factor < 6%) of differently substituted 4-cyclohexenones, all of them distributed in a rather limited conformational range, between envelope and half-chair/screw-boat conformations (Figure 4, Supporting Information). This is, of course, in contrast with perhydropyrimidinones **1**−**20**, encompassing essentially all regions of the conformational space (Tables 1 and 2; Figures 2 and 3).

1-Benzoyl-3-methylperhydropyrimidin-4-one, 2. This unsubstituted, "parent" pyrimidinone adopts a distorted half-chair conformation, where the C(2)−N(3)−C(4)−C(5) segment is quite planar owing to conjugation in the amide segment, while N(1) and C(6) are displaced away from the plane (Figure 5).

1-Benzoyl-(2*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one, (2*S*)-1. The crystal structure of a racemic sample was previously discussed.[8a,9a] The most salient observation is the quasi-axial orientation of the *tert*-butyl group, as a consequence of $A^{1,3}$ strain. The conformation of the ring is intermediate between a half-chair and an envelope, being closer to the latter (Figure 6a). Comparison with the crystal structure of **2** (see above) suggest that steric repulsion between one of the methyl groups of the axial *tert*-butyl and the methylene group at C(6) is responsible for the flattening of the heterocyclic ring, that is, the change from half-chair to envelope conformations upon incorporation of the *tert*-butyl group [**2** → (*S*)-**1**].

Replacement of the *tert*-butyl group by phenyl (**1** → **3**) does not produce significant changes in the ring conformation, intermediate between half-chair and envelope

Table 2. Conformational Parameters for Heterocycles 1−20, Calculated with the CP Method[b]

compd	Q	Q_2	Q_3	θ	ϕ	conformation
(2*S*)-**1**	0.430(3)	0.301(3)	−0.307(3)	44.4(5)	7.9(6)	between envelope and half-chair
2	0.473(2)	0.331(2)	−0.338(2)	44.4(3)	29.9(5)	distorted half-chair
rac-**3**	0.459(2)	0.323(2)	−0.326(3)	44.8(3)	13.1(4)	between envelope and half-chair
(2*S*)-**4**	0.493(4)	0.465(5)	−0.166(4)	70.4(5)	27.0(5)	distorted screw-boat
(2*S*)-**5**	0.457(4)	0.307(4)	−0.339(4)	42.2(5)	23.3(8)	between half-chair and envelope
(2*S*,6*R*)-**6**	0.507(4)	0.506(4)	−0.027(4)	86.9(5)	9.8(5)	between boat and twist
rac-**7**	0.593(2)	0.591(2)	0.051(2)	85.1(2)	15.5(2)	between twist and boat
rac-**8**	0.612(2)	0.612(2)	−0.007(2)	89.3(2)	6.2(2)	between boat and twist
(2*S*,6*S*)-**9**	0.584(5)	0.582(5)	−0.046(4)	85.5(4)	6.6(4)	between boat and screw-boat
(2*S*,6*S*)-**10**	0.456(2)	0.454(2)	−0.035(2)	85.6(3)	5.9(3)	between boat and screw-boat
(2*S*,6*S*)-**11**	0.503(3)	0.490(3)	0.111(3)	77.2(3)	17.2(3)	between screw-boat and boat
(2*R*,6*R*)-**12**	0.591(3)	0.579(2)	−0.119(2)	78.4(2)	22.3(3)	between twist and envelope
(2*S*,5*R*)-**13**	0.607(4)	0.604(4)	−0.057(4)	84.6(4)	18.6(4)	between twist and boat
(2*S*,5*R*)-**14**	0.447(3)	0.316(3)	−0.316(3)	45.0(4)	9.5(6)	between envelope and half-chair
rac-**15**	0.425(2)	0.361(2)	0.225(2)	58.1(3)	15.1(4)	between envelope and screw-boat
(2*S*,5*R*)-**16**	0.452(3)	0.352(3)	−0.283(3)	51.1(4)	8.3(4)	between envelope and half-chair
(2*S*,5*R*)-**17**	0.441(5)	0.295(5)	−0.327(5)	42.0(6)	19.5(9)	between half-chair and envelope
rac-**18**	0.550(3)	0.549(3)	0.026(3)	87.3(3)	8.7(3)	between boat and twist
rac-**19**	0.494(3)	0.489(3)	−0.070(3)	81.8(4)	16.4(4)	between screw-boat and boat
rac-**20**	0.690(2)	0.685(2)	0.078(2)	83.5(2)	6.5(2)	between boat and screw-boat

[b] Q = total puckering amplitude, $Q_2 = Q \sin\theta$, $Q_3 = Q \cos\theta$, θ = polar angle, ϕ = phase angle.

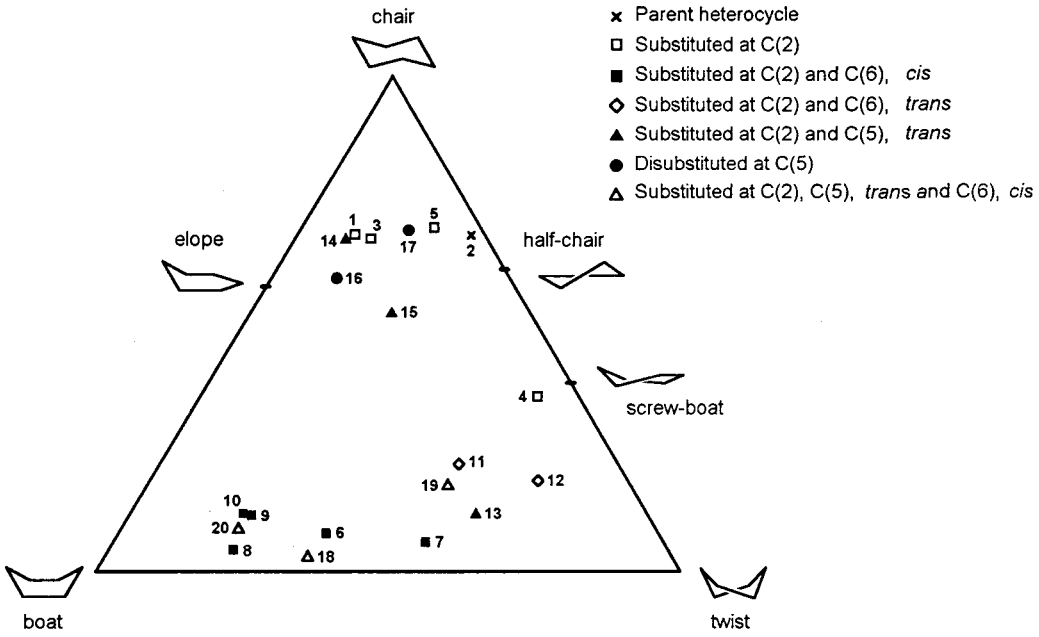


Figure 2. Distribution of pyrimidinones **1**−**20** in a three-component triangle diagram of the conformational space, obtained by the ZPD method. The triangle corresponds to a segment of the conformational sphere, where the canonical chair ($\theta = 0°$, $\psi = 0°$), boat ($\theta = 90°$, $\psi = 0°$), and twist-boat ($\theta = 90°$, $\psi = 30°$) are located at the triangle's corners.

but closer to the latter. If any, steric repulsion between the axial phenyl ring and the C(6) methylene decreases in **3** relative to **1**, as evidenced by a less pronounced flattening of the ring [C(4)−C(5)−C(6)−N(1) torsional angle = 38.3° in **3** versus 27.7° in **1**]. Also of interest is the orientation of the phenyl ring, almost eclipsed to the C(2)−N(3) bond [N(3)−C(2)−C_{ipso}−C_{ortho} = 16.8°] (Figure 6b).

5,5-Disubstituted (2*S*,5*R*)-**16** and (2*S*,5*R*)-**17** pyrimidinones suffer necessarily from steric repulsion between the axial *tert*-butyl group at C(2) and the syn substituent at C(5). Steric repulsion is minimized when the ring adopts an envelope conformation, as found in *rac*-**3**. (Figure 6c,d).

1-Benzoyl-(2*S*)-isopropyl-3-methylperhydropyrimidin-4-one, (2*S*)-4. This derivative exhibited the structure closest to a twist-boat (Figure 7). The isopropyl group is again in a pseudoaxial orientation (cf. *tert*-butyl group in **1** and phenyl group in **3**). Furthermore, the isopropyl group adopts an staggered conformation toward C(2)−N(1) and C(2)−N(3) bonds, with the C−H bond pointing inside the ring [H−C(15)−C(2)−N(1) torsional angle = 56.1° and H−C(15)−C(2)−N(3) = 68.8°]. Apparently, in the absence of any significant steric repulsion between the axial substituent at C(2) and the C(6) methylene group, the conformation of lowest energy is the twist-boat.

1-Benzoyl-(2*S*)-isopropylperhydropyrimidin-4-one, (2*S*)-5. The axial orientation of the isopropyl group at C(2) indicates that, as expected,[19] $A^{1,3}$ strain with the N(1)-benzoyl moiety is still sufficiently strong to overcome steric repulsion arising from the axial substituent. Nevertheless, removal of the N(3)-methyl group in going from (2*S*)-**4** to (2*S*)-**5** allows the C(2)−N(3)−C(4)−C(5) segment

(16) This program was supplied by D. Cremer in a personal communication.

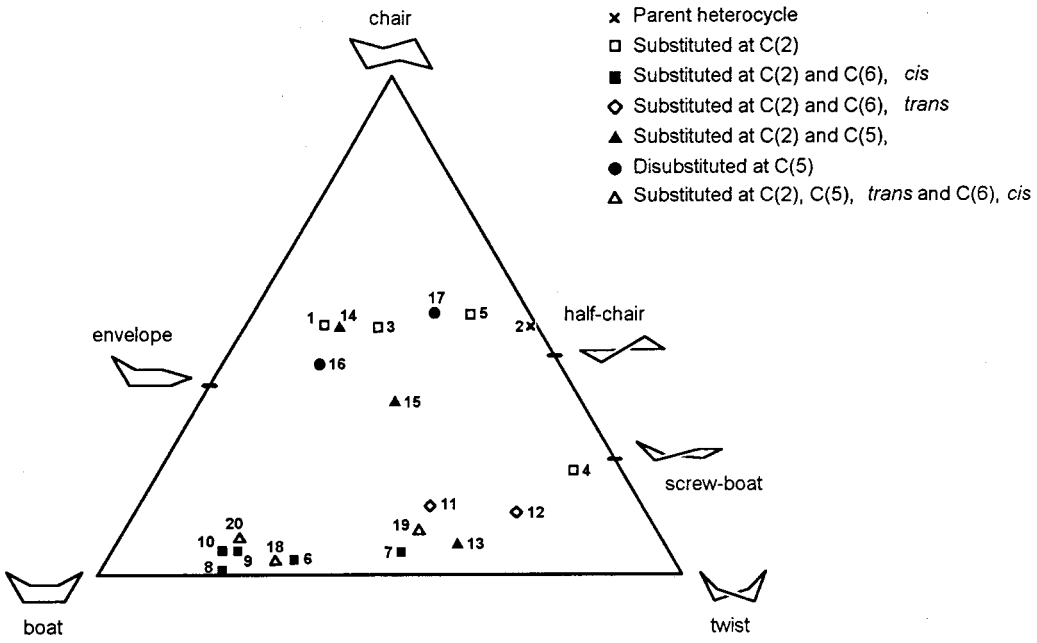


Figure 3. Distribution of pyrimidinones **1**−**20** in a three-component triangle diagram of the conformational space, obtained by the CP method. The triangle corresponds to a segment of the conformational sphere, where the canonical chair ($\theta = 0°$, $\psi = 0°$), boat ($\theta = 90°$, $\psi = 0°$), and twist-boat ($\theta = 90°$, $\psi = 30°$) are located at the triangle's corners.

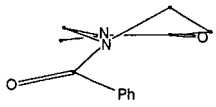


Figure 5. Structure and solid-state conformation of 1-benzoyl-3-methylperhydropyrimidin-4-one, **2** (schematic view).

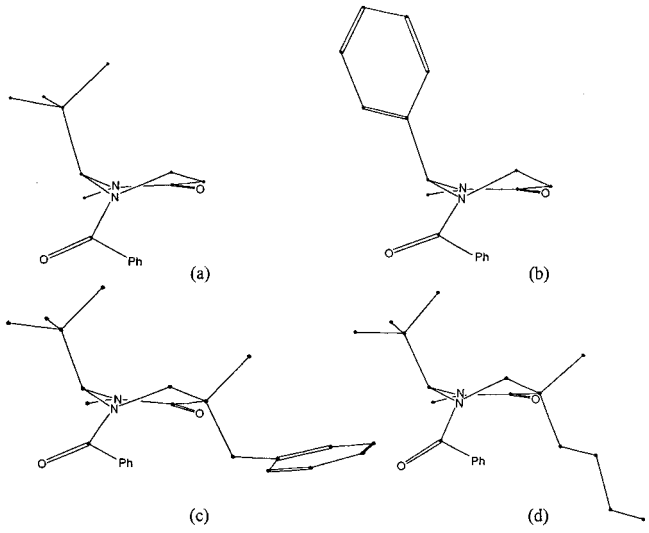


Figure 6. (a) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one, (2*S*)-**1**. (b) Structure and solid-state conformation of 1-benzoyl-2-phenyl-3-methylperhydropyrimidin-4-one, *rac*-**3**. (c) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-3,(5R)-dimethyl-5-benzylperhydropyrimidin-4-one, (2*S*,5*R*)-**16**. (d) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-3,(5*R*)-dimethyl-5-*n*-butylperhydropyrimidin-4-one, (2*S*,5*R*)-**17**.

to be flat, just like in the case of the parent, unsubstituted compound **2**; thus, (2*S*)-**5** adopts a half-chair ring conformation (Figure 8a). On the other hand, the isopropyl group adopts again an orientation with the C−H bond

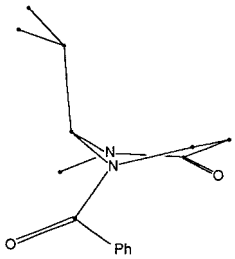


Figure 7. Structure and solid-state conformation of 1-benzoyl-(2*S*)-isopropyl-3-methylperhydropyrimidin-4-one, (2*S*)-**4**.

oriented toward the inside of the ring [cf. (2*S*)-**4**] (Figure 7).

1-Benzoyl-(2*S*)-*tert*-butyl-3-methyl-(5*R*)-benzylperhydropyrimidin-4-one, (2*S*,5*R*)-**14**, adopts a conformation very similar to that exhibited by (2*S*)-**5**, intermediate between a half-chair and an envelope. Apparently, no significant steric interaction arises between the trans benzyl group at C(5) and the *tert*-butyl group at C(2) (Figure 8b).

trans-**15** also exhibits a half-chair conformation, with a fairly flat C(2)−N(3)−C(4)−C(5) segment (torsional angle = 14.9°) because of the conjugation in the amide group (Figure 8c).

(17) The assumption that the situation in individual enantiomers and racemates is the same should be warranted for conglomerates. Racemic **3** and **20** fall in this category, so that their crystallographic structural data clearly correspond to those of enantiopure compounds. Nevertheless, we were able to confirm that structural data for racemic compounds *rac*-**1** and *rac*-**14** (CSD: JOPYUI and JOPZAP,[9a] respectively) are quite similar to those for enantiopure (2*S*)-**1** and (2*S*,5*R*)-**14**, as can be seen in Figure 21 and Table 6 (Supporting Information).

(18) This situation brings to mind the cyclohexane/cyclopentane contrastable behavior: In the six-membered ring one deals with a ring of essentially well-defined conformation, namely the chair form. By contrast, in the five-membered ring there are no pronounced energy minima. See: Willy, W. E.; Binsch, G.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 5394−5402.

(19) Breaking conjugation at the N−CO segment requires over 15 kcal/mol, whereas a bulky substituent axially disposed in the pyrimidinone ring requires less than 3−5 kcal/mol.

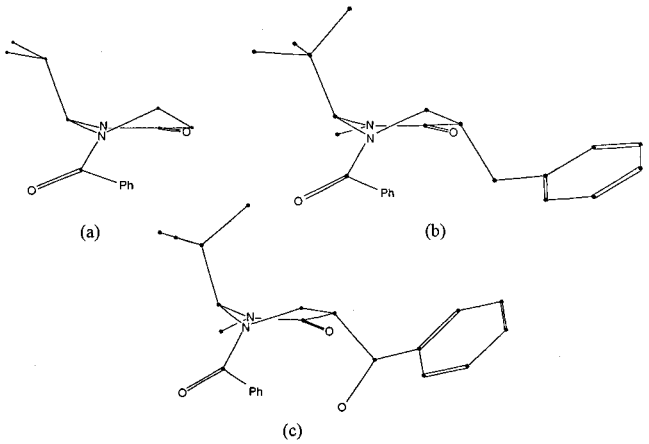


Figure 8. (a) Structure and solid-state conformation of 1-benzoyl-(2*S*)-isopropylperhydropyrimidin-4-one, (2*S*)-**5**. (b) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-3-methyl-(5R)-benzylperhydropyrimidin-4-one, (2*S*,5*R*)-**14**. (c) Structure and solid-state conformation of *rac-trans*-1-benzoyl-2-*tert*-butyl-5-hydroxybenzyl-3-methylperhydropyrimidin-4-one, *trans*-**15**.

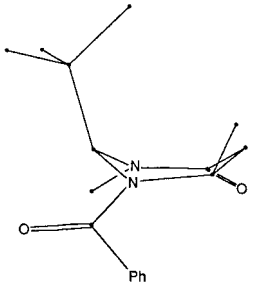


Figure 9. Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-3,(6*R*)-dimethylperhydropyrimidin-4-one, (2*S*,6*R*)-**6**.

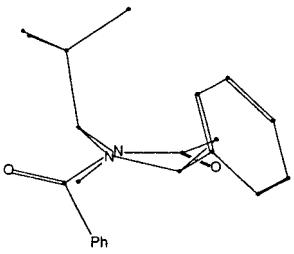


Figure 10. Structure and solid-state conformation of *rac-cis*-1-benzoyl-2-*tert*-butyl-3-methyl-6-phenylperhydropyrimidin-4-one, *cis*-**7**.

1-Benzoyl-(2*S*)-*tert*-butyl-3,(6*R*)-dimethylperhydropyrimidin-4-one, (2*S*,6*R*)-6. Derivatives of (2*S*)-**1** containing a syn substituent at C(6) avoid the large steric repulsion with the *tert*-butyl group by adopting boat or twist-boat ring conformations, where the C(6) substituent is pseudoequatorial (Figure 9).

***rac-cis*-1-Benzoyl-2-*tert*-butyl-3-methyl-6-phenylperhydropyrimidin-4-one, *cis*-7.** Upon substitution of the C(6)-methyl group by a bulkier phenyl group, the ring conformation changes from boat to twist-boat (cf. **6** → **7**), apparently to further minimize steric repulsion between the *tert*-butyl and phenyl substituents (Figure 10).

***rac-cis*-1-Benzoyl-2,6-diphenyl-3-methylperhydropyrimidin-4-one, *cis*-8.** The axial phenyl group at C(2) eclipses the C(2)−N(3) bond in order to reduce steric repulsion with the phenyl group at C(6). This objective is apparently achieved, since the ring conformation is again [cf. (2*S*,6*R*)-**6**] closer to an ideal boat form (Figure 11).

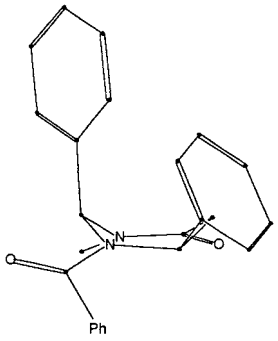


Figure 11. Structure and solid-state conformation of *rac-cis*-1-benzoyl-2,6-diphenyl-3-methylperhydropyrimidin-4-one, *cis*-**8**.

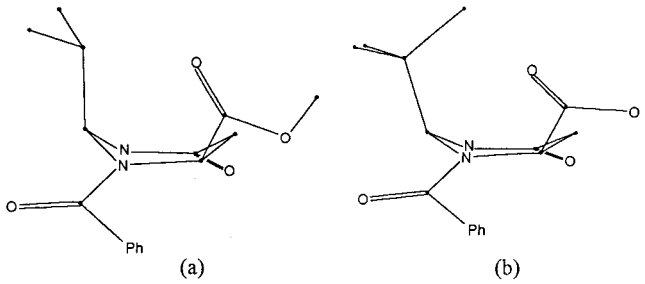


Figure 12. (a) Structure and solid-state conformation of 1-benzoyl-(2*S*)-isopropyl-(6*S*)-carbomethoxyperhydropyrimidin-4-one, (2**S**,6*S*)-**9**. (b) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-(6*S*)-carboxyperhydropyrimidin-4-one, (2*S*,6*S*)-**10**.

1-Benzoyl-(2*S*)-isopropyl-(6*S*)-carbomethoxyperhydropyrimidin-4-one, (2*S*,6*S*)-9. The lack of significant steric repulsion between the axial isopropyl group at C(2) and the syn carbomethoxy group at C(6) allows for the ring conformation to exist again [cf. (2*S*,6*R*)-**6** and *cis*-**8**] in a boat shape (Figure 12a).

By the same token, steric repulsion between the *tert*-butyl and carboxylic groups is minimized in the boat conformation of (2*S*,6*S*)-**10** (Figure 12b).

1-Benzoyl-(2*S*)-*tert*-butyl-(6*S*)-methoxyperhydropyrimidin-4-one, (2*S*,6*S*)-11. Since the axial *tert*-butyl group at C(2) and the methoxy substituent at C(6) are trans to each other, no steric repulsion between these groups can be anticipated. Nevertheless, the ring adopts a conformation intermediate between boat and twist-boat, probably to benefit from an $n_N \rightarrow \sigma^*_{C-O}$ hyperconjugative interaction[5] that would not be feasible in the envelope or half-chair conformations (Figure 13a). An alternative or complementary rationalization for the axial orientation of the methoxy group is that a ring conformation with equatorial methoxy would cause increased gauche repulsion ($A^{1,3}$ strain) with the adjacent N(1)-benzoyl group.

The ring conformation in (2*R*,6*R*)-**12** is quite similar to that observed in (2*S*,6*S*)-**11**, between twist and envelope (Figure 13b). The methyl group at C(6) adopts an axial orientation as a consequence of $A^{1,3}$ strain with the *N*-benzoyl group.

1-Benzoyl-(2*S*)-isopropyl-3,(5*R*)-dimethylperhydropyrimidin-4-one, (2*S*,5*R*)-13. The twist form adopted by this heterocycle permits the methyl substituent at C(5)

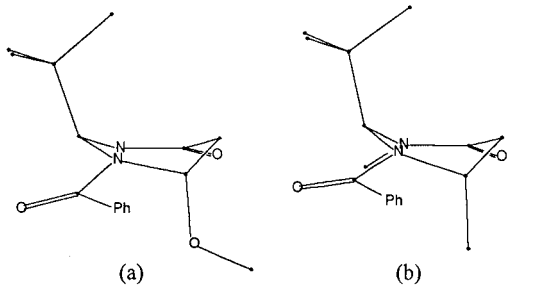


Figure 13. (a) Structure and solid-state conformation of 1-benzoyl-(2*S*)-*tert*-butyl-(6*S*)-methoxyperhydropyrimidin-4-one, (2*S*,6*S*)-**11**. (b) Structure and solid-state conformation of 1-benzoyl-(2*R*)-*tert*-butyl-3,(6*R*)-dimethylperhydropyrimidin-4-one, (2*R*,6*R*)-**12**. (This figure corresponds to the enantiomeric structure, to facilitate the analysis).

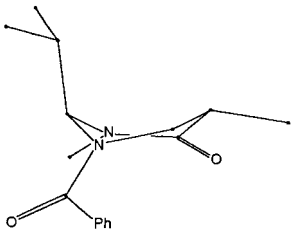


Figure 14. Structure and solid-state conformation (schematic view) of 1-benzoyl-(2*S*)-isopropyl-3,(5*R*)-dimethylperhydropyrimidin-4-one, (2*S*,5*R*)-**13**.

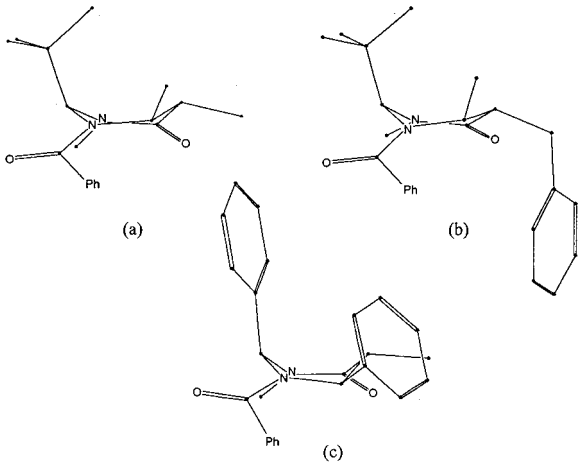


Figure 15. (a) Structure and solid-state conformation of *rac*-1-benzoyl-r-2-*tert*-butyl-3,*trans*-5,*cis*-6-trimethylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-**18**. (b) Structure and solid-state conformation of *rac*-1-benzoyl-*r*-2-*tert*-butyl-3,*cis*-6-dimethyl-*trans*-5-benzylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-**19**. (c) Structure and solid-state conformation of *rac*-1-benzoyl-*r*-2-phenyl-3,*trans*-5-dimethyl-*cis*-6-phenylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-**20**.

to occupy an equatorial orientation. The isopropyl group at C(2) is axial and staggered with all three remaining bonds at C(2). The C−H bond at the isopropyl group points inside the six-membered ring. (Figure 14).

***rac*-*r*-2-*tert*-Butyl-*trans*-5,*cis*-6-trisubstituted Derivatives, 18−20.** Intermediate conformations between boat and twist-boat were encountered in these heterocycles, which seem plausible since now both the substituents at C(5) and C(6) are equatorially oriented (Figure 15).

One wonders, of course, what happens in solution. In principle, ^{1}H NMR spectroscopic analysis should allow

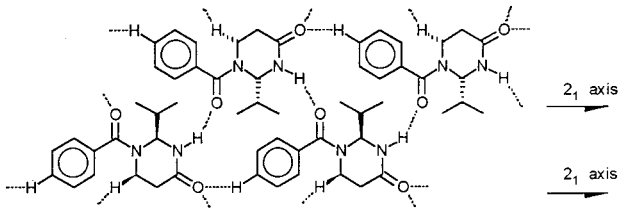


Figure 17. Schematic view of the crystal packing in (2*S*)-**5** (see text).

assignment of ring conformation from the determination of coupling constants between vicinal hydrogens. In the case of compounds **1**−**20**, measurement of $J_{H(5)H(6)}$ is complicated by the manifestation of dynamic phenomena that give rise to broad spectra. Nevertheless, good agreement was found between the experimentally measured (solution ^{1}H NMR spectroscopy) and calculated (by means of Altona's algorithm,[20] using the solid-state structural data) *J*'s for *rac*-**3** (Table 3, Supporting Information). By contrast, in the case of (2*S*)-**4**, comparison between the computed coupling constants and those extracted from the ^{1}H NMR spectra is obliterated by conformational averaging owing to small energy differences among two or more ring conformers.

In this regard, a stochastic conformational search[21] with Allinger's MM3(94) program[22] afforded three conformations of minimum energy for compound **2**. (Figure 16, Supporting Information). Energy differences between these conformations are very small (ΔE = 0.3−0.6 kcal/mol), supporting the X-ray crystallographic evidence for a highly flexible perhydropyrimidinone ring that adjusts itself easily to the requirements of the substituents.

Finally, there is the question of potential hydrogen bonding in (2*S*)-**5**, (2*S*,6*S*)-**9**, (2*S*,6*S*)-**10**, and (2*S*,6*S*)-**11**. In particular, one wonders what role might intermolecular hydrogen bonding/crystal packing play in the conformation of these compounds.

Analysis of the unit cell composition in the crystal structure of (2*S*)-**5** reveals the existence of an intermolecular hydrogen bonding between N(3)−H and the benzoyl carbonyl of an adjacent molecule (r = 2.14 Å). Two additional intermolecular interactions were observed, between the *para*-hydrogen on the benzoyl ring and the endocyclic carbonyl of an adjacent molecule (r = 2.48 Å) and between C(6)−H_{ax} and the endocyclic carbonyl of a vicinal molecule (r = 2.37 Å). As a consequence of these interactions, each pyrimidinone molecule is hydrogen bonded to six adjacent molecules (Figure 17).

The X-ray crystallographic structure of (2*S*,6*S*)-**9** also provides evidence for strong hydrogen bonding between N(3)−H and the benzoyl carbonyl of an adjacent molecule (r = 2.20 Å). Surprisingly, the methoxy oxygen seems to interact with an isopropyl hydrogen of a vicinal molecule, as the H- - -O distance is only 2.53 Å (Figure 18, Supporting Information).

(2*S*,6*S*)-**10** presents two types of intermolecular hydrogen bonding, (1) between N(3)−H and the carboxy carbonyl (r = 2.06 Å) and (2) between the carboxylic

(20) (a) Cerda-García-Rojas, C. M.; Zepeda, L. G.; Joseph-Nathan, P. *Tetrahedron Comput. Methodol.* **1990**, *3*, 113−118. (b) Haasnoot, C. A. G.; M. de Leeuw, F. A. A.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(21) Saunders, M. *J. Am. Chem. Soc.* **1987**, *109*, 3150−3152.

(22) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551−8566.

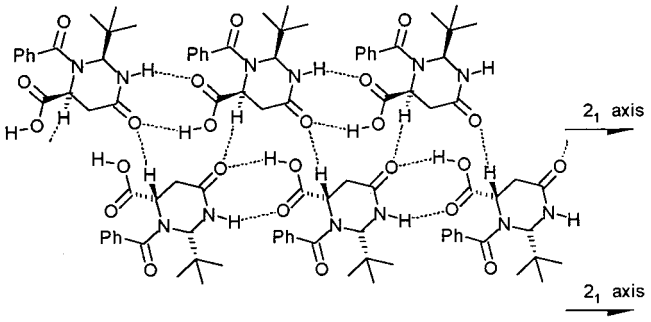


Figure 19. Schematic view of the crystal packing in (2*S*,6*S*)-**10** (see text).

group OH and the endocyclic carbonyl of an adjacent molecule ($r = 1.77$ Å). Thus, each molecule binds to two additional molecules in the unit cell, giving rise to chains that are bonded themselves through H(6) and C(4)−O (Figure 19).

Analysis of the crystal packing in (2*S*,6*S*)-**11** reveals intermolecular hydrogen bonding between N(3)−H and the endocyclic carbonyl of an adjacent molecule ($r = 2.07$ Å), giving rise to an infinite chain. A weaker intermolecular interaction exists between the same endocyclic carbonyl and C(5)−H_{eq} of a vicinal molecule ($r = 2.55$ Å) (Figure 20, Supporting Information).

Conclusions

Precise conformational analysis of 20 substituted perhydropyrimidinones was carried out by X-ray crystal structure determination and quantitative examination of the atomic coordinates by means of the CP and ZPD computer programs. Both methods provide convincing evidence that the perhydropyrimidin-4-one ring conformation proved extremely sensitive to substitution. The parent, unsubstituted system **2** adopts a half-chair conformation, which is maintained in strain-free derivatives **5** and **14**, where $A^{1,3}$ strain forces the C(2) substituent to occupy the axial orientation. Nevertheless, introduction of a syn group at C(5) as in **16** and **17** causes sufficient steric repulsion to compel the ring to choose an envelope conformation. On the other hand, the steric strain provoked upon incorporation of syn substituents at C(6) is relieved in the boat conformations exhibited by **6**−**10**. In this regard, derivative **11** presents a methoxy group anti (rather than syn) to the C(2) *tert*-butyl. The boat ring conformation here allows for $n_N \rightarrow \sigma^*_{C-O}$ stabilizing hyperconjugation and minimizes $A^{1,3}$ allylic-type strain between the methoxy and N(1)-benzoyl groups. Twist-boat conformations are preferred by **4**, where removal of the N(3) methyl eliminates strain with the axial isopropyl group at C(2), and by **18**−**20**, where the twist-boat form allows for the diequatorial disposition of both C(5) and C(6) substituents.

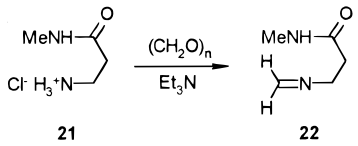
Experimental Section

General Methods. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for about 12 h at 120 °C. Anhydrous THF was obtained by distillation from benzophenone ketyl.[23] The *n*-butyllithium employed was titrated according to the method of Juaristi et al.[24] (4-biphenylmethanol indicator).

TLC: F_{254} silica gel plates; detection by UV light or iodine vapor. Flash column chromatography:[25] silica gel (230−400 mesh). Melting points: not corrected. ^{1}H NMR spectra: 60, 270, and 400 MHz spectrometers. ^{13}C NMR: 22.5, 67.8, and 100 MHz spectrometers. Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (J) are given in Hz. Optical rotations were measured in a polarimeter, using the sodium D-line (589 nm). Mass spectra: 70 eV. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Syntheses. The syntheses of 1-benzoyl-(2*S*)-*tert*-butyl-3-methyl-perhydropyrimidin-4-one, (2*S*)-**1**,[8b] 1-benzoyl-(2*S*)-*tert*-butyl-(6*S*)-carboxyperhydropyrimidin-4-one, (2*S*,6*S*)-**10**,[8b] 1-benzoyl-(2*S*)-*tert*-butyl-3-methyl-(5*R*)-benzylperhydropyrimidin-4-one, (2*S*,5*R*)-**14**,[8b] 1-benzoyl-(2*S*)-*tert*-butyl-3,(6*R*)-dimethylperhydropyrimidin-4-one, (2*S*,6*R*)-**6**,[26] 1-benzoyl-(2*R*)-*tert*-butyl-3,(6*R*)-dimethylperhydropyrimidin-4-one, (2*R*,6*R*)-**12**,[26] *rac*-1-benzoyl-*r*-2-*tert*-butyl-3,*trans*-5,*cis*-6-trimethylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-**18**,[26] *rac*-1-benzoyl-*r*-2-*tert*-butyl-3,*cis*-6-dimethyl-*trans*-5-benzylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-**19**,[26] 1-benzoyl-(2*S*)-isopropyl-(6*S*)-carbomethoxyperhydropyrimidin-4-one, (2*S*,6*S*)-**9**,[26] 1-benzoyl-(2*S*)-*tert*-butyl-3,(5*R*)-dimethyl-5-benzylperhydropyrimidin-4-one, (2*S*,5*R*)-**16**,[8c] and 1-benzoyl-(2*S*)-*tert*-butyl-3,(5*R*)-dimethyl-5-*n*-butylperhydropyrimidin-4-one, (2*S*,5*R*)-**17**,[8c] have been described in the literature.

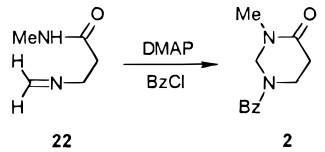
3-(Methylideneamino)-*N*-methylpropionamide, 22:



21 **22**

Methyl 3-aminopropionamide hydrochloride[8a] (**21**, 9.5 g, 69 mmol) and 19.0 mL (137 mmol) of triethylamine in 50 mL of CH_2Cl_2 were placed in a round-bottom flask provided with a magnetic stirrer and treated dropwise with 6.12 g (204 mmol) of paraformaldehyde. The reaction mixture was heated to reflux for 4 h, with an inverse Dean−Stark trap being used to collect the water that was generated. The triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to afford 5.56 g (71.7% yield) of the desired imine as a pale-yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.40 (t, J = 5.8 Hz, 2H), 2.90 (s, 3H), 2.75−3.25 (m, 2H), 4.10 (br s, 2H).

1-Benzoyl-3-methylperhydropyrimidin-4-one, 2:



22 **2**

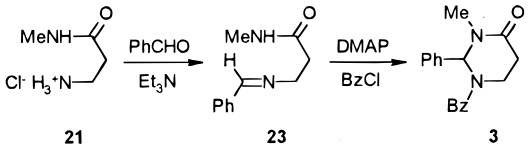
3-(Methylideneamino)-*N*-methylpropionamide (**22**, 5.0 g, 43 mmol) in 150 mL of dry benzene was treated with 4.72 g (38 mmol) of DMAP and 5.5 mL (47 mmol) of benzoyl chloride (dropwise addition) and heated to reflux for 4 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotary evaporator. The residue was separated by flash chromatography (hexanes−ethyl acetate, 70:30 → 10:90) to afford 7.4 g (81.5% yield) of **2** as a viscous colorless oil, which was slowly crystallized from hexanes−ethyl acetate (9:1), mp 72.5−73.5 °C: ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ 2.43 (t, J = 6.6 Hz, 2H), 2.81 (s,

(23) Brown, H. C.; Kramer, G. W.; Levy A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 256.
(24) Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603−2606.
(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(26) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396−2398.

3H), 3.71 (t, J = 6.6 Hz, 2H), 4.83 (s, 2H), 7.47 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6, 100 °C) δ 31.9, 32.2, 42.0, 61.1, 127.4, 128.9, 130.6, 135.6, 167.9, 169.9; MS, *m/z* 218 (M^+), 161, 105, 98, 77, 51, 42.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47. Found: C, 65.83; H, 6.67.

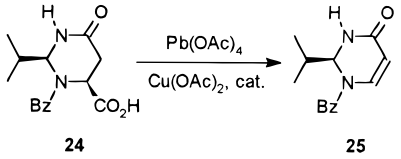
***rac*-1-Benzoyl-2-phenyl-3-methylperhydropyrimidin-4-one, *rac*-3:**



21 **23** **3**

Methyl 3-aminopropionamide hydrochloride[8a] (**21**, 0.5 g, 3.6 mmol) and 0.75 mL (5.4 mmol) of triethylamine in 35 mL of CH_2Cl_2 were treated dropwise with 0.4 mL (3.9 mmol) of benzaldehyde. The reaction mixture was heated to reflux for 5 h, with azeotropic removal of water. The triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to afford 0.7 g (100% yield) of the imine **23**, which was immediately dissolved in dry benzene and treated dropwise with 0.39 g (3.2 mmol) of DMAP and 0.51 g (3.6 mmol) of benzoyl chloride. The reaction mixture was heated to reflux for 4 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotary evaporator. The residue was separated by flash chromatography (hexanes−ethyl acetate, 90:10 → 10:90) to afford 0.34 g (31.8% two step yield) of *rac*-3 as a white solid which was recrystallized from CH_2Cl_2−hexane, mp 138−139 °C: ^{1}H NMR (270 MHz, 60 °C, $CDCl_3$) δ 2.39 (ddd, J_{gem} = 17.6 Hz, J_{gauche} = 5.4 Hz, J_{gauche} = 2.2 Hz, 1H), 2.59 (ddd, J_{gem} = 17.6 Hz, J_{anti} = 11.1 Hz, J_{gauche} = 7. 7 Hz, 1H), 2.96 (s, 3H), 3.21 (ddd, J_{gem} = 13.9 Hz, J_{anti} = 11.1 Hz, J_{gauche} = 5.4 Hz, 1H), 3.75 (br s, 1H), 6.82 (br s, 1H), 7.36−7.42 (m, 10H); ^{13}C NMR (270 MHz, 60 °C, $CDCl_3$) δ 31.8, 33.4, 38.6, 70.0, 126.6, 126.8, 128.7, 129.0, 129.1, 130.4, 134.8, 137.2, 167.7, 170.0.

1-Benzoyl-(2*S*)-isopropy1-2,3-dihydro-4(1*H*)-1,3-pyrimidin-4-one, (2*S*)-25:



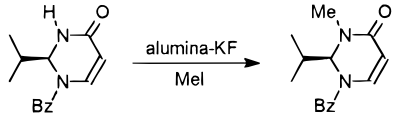
24 **25**

In a round-bottom flask provided with magnetic stirrer, 10.0 g (34.5 mmol) of 1-benzoyl-(2*S*)-isopropyl-(6*S*)-carboxyperhydropyrimidin-4-one,[27] (2*S*,6*S*)-**24**, was dissolved in 100 mL of benzene and 60 mL of THF containing 5 mL of pyridine. The resulting solution was treated with 0.25 g (1.2 mmol) of copper diacetate monohydrate, and the mixture was stirred at ambient temperature for 2 h. The reaction flask was then submerged in an ice−water bath before the addition of 27 g (60.9 mmol) of lead tetraacetate. The cooling bath was removed, and the reaction mixture was heated to reflux for 12 h. The precipitate was removed by filtration, and the filtrate was percolated over silica gel, using ethyl acetate as solvent. The desired product was purified by crystallization from ethyl acetate−hexane (7:3) to afford 5.46 g (75.9% yield) of (*S*)-**25** as a white solid, mp 155−156 °C: $[\alpha]_D$ = +522.5 (c = 1, $CHCl_3$); ^{1}H NMR (DMSO-d_6; 80 °C; 270 MHz) δ 0.88 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 2.21 (m, 1H), 5.13 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 5.41 (m, 1H), 7.10 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1H), 7.47−7.60 (m, 5H), 8.00 (br s, 1H); ^{13}C NMR (DMSO-d_6; 80 °C; 67.8 MHz) δ 17.7, 18.3, 32.7, 68.4, 105.2, 127.8, 128.7, 131.0, 133.5, 137.1, 162.3, 168.2.

(27) Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706−4710.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.82; H, 6.60. Found: C, 68.59; H, 6.73.

1-Benzoyl-(2*S*)-isopropy1−3-methyl-2,3-dihydro-4(1*H*)-1,3-pyrimidin-4-one, (2*S*)-26:

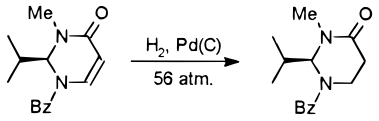


25 **26**

In a round-bottom flask, provided with a magnetic stirrer, 3.2 g (13.1 mmol) of (*S*)-**25** and 37 mL of dimethoxyethane (DME) were placed. The flask was submerged in an ice−water bath before the dropwise addition of 10 g of alumina−KF. The resulting mixture was stirred for 1 h and then treated with 2.12 mL (34.1 mmol) of methyl iodide. The reaction mixture was stirred at 0 °C for 2 h and 48 h more at ambient temperature before the slow addition of 20 mL of chloroform. The alumina was removed by filtration, and the filtrate was concentrated on a rotary evaporator. The desired product was purified by flash chromatography (ethyl acetate−hexane, 7:3) and crystallized from ethyl ether−hexane to afford 2.46 g (72% yield) of (2*S*)-**26**, mp 103−104 °C: $[\alpha]_D$ = +509.9 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 270 MHz) δ 0.98 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 2.48 (double of septets, J_1 = 6.6 Hz, J_2 = 7.9 Hz, 1H), 3.17 (s, 3H), 5.37 (d, J = 7.9 Hz, 1H), 5.66 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 7.50 (m, 5H); ^{13}C NMR ($CDCl_3$; 22.49 MHz) δ 18.7, 19.1, 32.3, 35.9, 74.8, 106.3, 128.1, 128.6, 131.4, 132.8, 135.9, 162.3, 168.4.

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 70.04; H, 7.33.

1-Benzoyl-(2*S*)-isopropyl-3-methylperhydropyrimidin-4-one, (2*S*)-4:

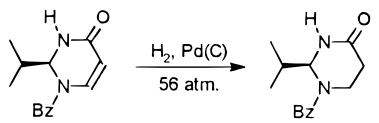


26 **4**

Heterocycle (2*S*)-**26** (1.0 g, 3.9 mmol), 10 mL of methanol, and 0.1 g of 5% Pd(C) were placed in a hydrogenation flask. The reaction mixture was pressurized to 56 atm of hydrogen, heated to 70 °C, and stirred for 4.5 h. The catalyst was then removed by filtration over Celite, and the filtrate was evaporated at reduced pressure. The residue was crystallized from ethyl acetate−hexane (1:9) to give 1.0 g (100% yield) of (2*S*)-**4** as a white solid, mp 101−102 °C. $[\alpha]_D$ = +21.0 (c = 1.02; $CHCl_3$); ^{1}H NMR (DMSO-d_6; 130 °C; 270 MHz) δ 0.92 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 2.32 (double of septets, J = 9.8 Hz, J = 7.0 Hz, 1H), 2.48 (ddd, J = 7.7 Hz, J = 8.8 Hz, J_{gem} = 17.6 Hz, 1H), 2.70 (ddd, J = 7.7 Hz, J = 5.1 Hz, J_{gem} = 17.6 Hz, 1H), 2.92 (s, 3H), 3.56 (ddd, J = 7.7 Hz, J = 7.7 Hz, J_{gem} = 13.6 Hz, 1H), 3.84 (dddd, J = 8.8 Hz, J = 5.1 Hz, J = 0.7 Hz, J_{gem} = 13.6 Hz, 1H), 5.12 (dc, J = 9.8 Hz, J = 0.7 Hz, 1H), 7.35−7.49 (m, 5H); ^{13}C NMR (DMSO-d_6; 100 °C; 67.8 MHz) δ 18.2, 18.2, 29.3, 32.1, 64.5, 38.9, 73.6, 126.1, 127.9, 129.2, 135.1, 166.4, 169.1.

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74. Found: C, 69.06; H, 7.49.

1-Benzoyl-(2*S*)-isopropylperhydropyrimidin-4-one, (2S)-5:

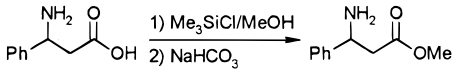


25 **5**

Heterocycle (2*S*)-**25** (1.0 g, 4.2 mmol), 10 mL of methanol, and

0.1 g of 5% Pd(C) was placed in a hydrogenation flask. The reaction mixture was pressurized to 56 atm of hydrogen, heated to 70 °C, and stirred for 4.5 h. The catalyst was then removed by filtration over Celite, and the filtrate was evaporated at reduced pressure. The residue was crystallized from ethyl acetate−hexane (2:8) to give 1.0 g (100% yield) of (2*S*)-**5** as a white solid, mp 142−144 °C. $[\alpha]_D = +71.45$ ($c = 1.03$; $CHCl_3$); ^{1}H NMR (DMSO-d_6; 130 °C; 270 MHz) δ 0.88 (d, $J =$ 6.6 Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 2.10 (double of septets, $J = 6.6$ Hz, $J = 8.8$ Hz, 1H), 2.25 (ddd, $J = 3.6$ Hz, $J = 6.6$ Hz, $J_{gem} = 16.7$ Hz, 1H), 2.34 (ddd, $J = 7.3$ Hz, $J = 9.4$ Hz, $J_{gem} = 16.7$ Hz, 1H), 3.43 (ddd, $J = 10.4$ Hz, $J = 7.0$ Hz, J_{gem} = 14.0 Hz, 1H), 3.86 (ddd, $J = 3.5$ Hz, $J = 7.0$ Hz, $J_{gem} = 14.0$ Hz, 1H), 5.06 (d, $J = 8.8$ Hz, 1H), 7.35−7.47 (m, 5H), 7.78 (br s, 1H); ^{13}C NMR (DMSO-d_6; 130 °C; 67.8 MHz) δ 18.2, 18.6, 30.8, 33.4, 37.9, 67.7, 126.5, 128.5, 129.7, 135.9, 167.8, 169.7.

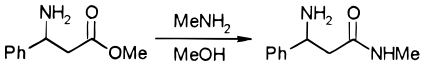
Methyl 3-Amino-3-phenylpropionate, *rac*-27:



27

3-Amino-3-phenylpropionic acid[28] (5 g, 30 mmol) in 100 mL of methanol was placed in a round-bottom flask provided with an addition funnel and a magnetic stirrer. The solution was cooled to 0 °C and treated dropwise with 10 mL (83 mmol) of trimethylsilyl chloride. The reaction mixture was stirred at ambient temperature for 12 h and concentrated in a rotary evaporator. For the liberation of the hydrochloride the residue was dissolved in 10 mL of distilled water and then treated with $NaHCO_3$ until pH 8. The aqueous phase was extracted with five portions of 5 mL of ethyl acetate, and the combined extracts were dried (NaCl), filtered, and evaporated to give 5.32 g (100% yield) of *rac*-**27**, mp 148−149 °C (as the hydrochloride): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.75 (s, 2H), 2.62 (d, $J = 7$ Hz, 2H), 3.55 (s, 3H), 4.32 (t, $J = 7$ Hz, 1H), 7.25 (s, 5H).

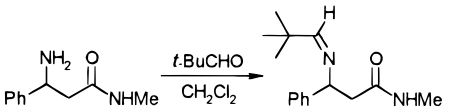
***N*-Methyl-3-amino-3-phenylpropionamide, *rac*-28:**



27 28

A 5 g (27 mmol) amount of methyl 3-amino-3-phenylpropionate, *rac*-**27**, in 15 mL of methanol was placed in a round-bottom flask provided with a magnetic stirrer and an addition funnel. The solution was cooled to 0 °C and treated dropwise with 8.4 mL (108 mmol) of aqueous 40% methylamine. The resulting mixture was stirred at ambient temperature for 40 h and concentrated in a rotary evaporator to give 4.8 g (100% yield) of the desired product, *rac*-**28**, as a pale-yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.20 (br s, 2H), 2.43 (d, $J = 7$ Hz, 2H), 2.65 (d, $J = 5$ Hz, 3H), 4.28 (t, $J = 7$ Hz, 1H), 7.22 (m, 5H).

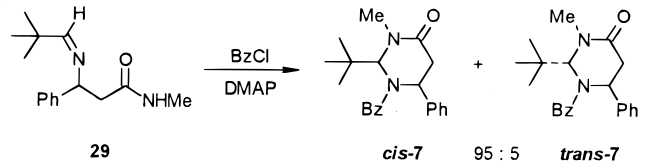
3-Phenyl-3-*N*-(2′,2′-dimethylpropylidene)amino-*N*-methylpropionamide, *rac*-29:



28 29

N-Methyl-3-amino-3-phenylpropionamide (*rac*-**28**, 4.5 g, 25 mmol) in 50 mL of CH_2Cl_2 was placed in a round-bottom flask provided with an addition funnel and a magnetic stirrer. The resulting solution was treated dropwise with 5.4 mL (50 mmol) of pivalaldehyde, and the reaction mixture was heated to reflux for 5 h, with azeotropic removal of water. Concentration of the mixture on a rotary evaporator afforded 5.52 g (89.7% yield) of *rac*-**29**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.08 (s, 9H), 2.4−2.9 (m, 2H), 2.68 (s, 3H), 4.52 (t, $J = 7$ Hz, 1H), 6.4 (br s, 1H), 7.21 (m, 5H), 7.5 (s, 1H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 25.7, 26.7, 36.1, 45.3, 69.9, 126.3, 126.8, 128.3, 142.7, 171.2, 172.9.

***rac-cis*- and *rac-trans*-1-Benzoyl-2-*tert*-butyl-3-methyl-6-phenylperhydropyrimidin-4-one, *rac-cis*-7 and *rac-trans*-7:**



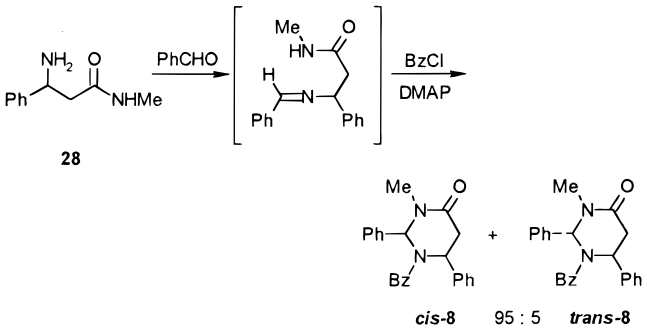
29 *cis*-7 95 : 5 *trans*-7

3-Phenyl-3-*N*-(2′,2′-dimethylpropilidene)amino-*N*-methylpropionamide (*rac*-**29**, 4.69 g, 19 mmol) and 100 mL of dry benzene was treated with 2.08 g (17 mmol) of DMAP and 2.4 mL (20 mmol) of benzoyl chloride (dropwise addition). The reaction mixture was heated to reflux for 4 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotary evaporator to afford 7.5 g of the crude product, consisting of a 95:5 mixture of cis and trans diastereomeric heterocycles. The mixture was separated by flash chromatography (hexanes−ethyl acetate, 90:10 → 10:90) to afford 569 mg of *rac-cis*-**7** and 30 mg of *rac-trans*-**7** (a combined yield of 9%).

rac-cis-**7**: mp 174−175 °C; ^{1}H NMR (270 MHz, $CDCl_3$, 60 °C) δ 1.10 (s, 9H), 2.87 (dd, $J_1 = 16.5$ Hz, $J_2 = 7.3$ Hz, 1H), 3.03 (dd, $J_1 = 16.5$ Hz, $J_2 = 11.9$ Hz, 1H), 3.16 (s, 3H), 5.31 (dd, $J_1 = 11.9$ Hz, $J_2 = 7.3$ Hz, 1H), 5.68 (s, 1H), 7.02−7.19 (m, 10H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 28.1, 38.3, 38.8, 40.5, 56.7, 80.1, 125.6, 127.0, 128.1, 128.5, 128.7, 136.8, 141.9, 169.0, 173.7.

rac-trans-**7**: mp 70−71 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.20 (s, 9H), 2.42 (dd, $J_1 = 16.5$ Hz, $J_2 = 1.3$ Hz, 1H), 3.25 (s, 3H), 3.41 (dd, $J_1 = 16.5$ Hz, $J_2 = 7.3$ Hz, 1H), 5.26 (dd, $J_1 = 7.3$ Hz, $J_2 = 1.3$ Hz, 1H), 6.16 (s, 1H), 6.63−6.65 (m, 2H), 6.96−7.32 (m, 8H); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 28.2, 38.4, 39.7, 42.1, 59.1, 77.0, 125.0, 126.4, 127.3, 128.1, 128.8, 129.7, 136.8, 143.6, 168.2, 173.9.

***rac-cis*- and *rac-trans*-1-Benzoyl-2,6-diphenyl-3-methylperhydropyrimidin-4-one, *rac-cis*-8 and *rac-trans*-8:**



28 *cis*-8 95 : 5 *trans*-8

N-Methyl-3-amino-3-phenylpropionamide (*rac*-**28**, 2.2 g, 12 mmol) and 100 mL of CH_2Cl_2 were placed in round-bottom flask provided with a magnetic stirrer and treated dropwise with 1.48 g (14 mmol) of benzaldehyde. The reaction mixture was heated to reflux for 5 h and then treated with 1.46 g (12 mmol) of DMAP and 1.84 g (13 mmol) of benzoyl chloride. The reaction mixture was heated to reflux for 4 h additional hours. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotary evaporator to afford 5.2 g of the crude product, consisting of a 95:5 mixture of cis and trans diastereomeric heterocycles. The mixture was separated by flash chromatography (hexanes−ethyl acetate, 90:10 → 10:90) to afford 1.71 g of *rac-cis*-**8** and

(28) Rault, S.; Dallemagne, P.; Robba, M. *Bull Soc. Chim. Fr.* **1987**, *6*, 1079.

0.09 g of *rac-trans*-**8**. (A combined yield of 41.3%.) Both heterocycles were recrystallized from CH_2Cl_2-hexane.

rac-cis-**8**: mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (dd, J_{gem} = 15.7 Hz, J_{gauche} = 5.9 Hz, 1H), 2.75 (dd, J_{gem} = 15.7 Hz, J_{anti} = 11.0 Hz, 1H), 3.21 (s, 3H), 5.20 (br s, 1H), 6.53 (br s, 1H), 6.95−7.39 (m, 15H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 34.22, 39.13, 58.19, 71.26, 125.92, 126.36, 126.53, 127.26, 128.30, 128.47, 128.67, 129.16, 129.47, 135.94, 138.15, 140.52, 169.30, 172.48.

rac-trans-**8**: mp 166−167 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.42 (dd, J_{gem} = 15.6 Hz, J_{gauche} = 1.9 Hz, 1H), 2.93 (dd, J_{gem} = 15.6 Hz, J_{anti} = 6.9 Hz, 1H), 3.34 (s, 3H), 5.24 (d, J_{anti} = 6.7 Hz, 1H), 6.86 (br s, 1H), 7.13−7.41 (m, 15H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 34.90, 39.37, 57.67, 71.38, 125.37, 126.19, 127.65, 128.35, 128.66, 128.89, 129.42, 135.97, 139.47, 142.25, 168.68, 171.94.

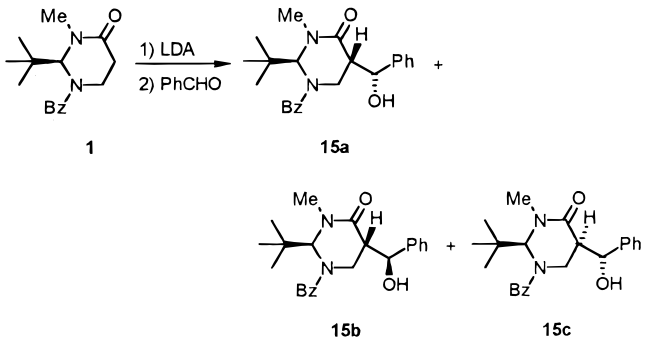
1-Benzoyl-(2*S*)-*tert*-butyl-(6*S*)-methoxyperhydropyrimidin-4-one, (2*S*,6*S*)-11. In a glass cell for electrolysis were placed 82 mL of a solution 0.1 M of (2*S*,6*S*)-**10** (2.5 g, 8.2 mmol) in methanol. The anode was placed in a rotor with a disk of platinum (area 4.25 cm^2) and the cathode in a grill of platinum, separated by 5 mm. The electrode was rotated at 2000 rpm while the temperature of the reaction mixture was maintained between 15 and 20 °C, and a voltage of 7 V was applied while 0.5 mL of triethylamine was added dropwise, producing a current of 350 mA, equivalent to a current density of 82 mA/cm^2. The reaction was followed by TLC until complete consumption of the starting material (5 h) and then concentrated in a rotary evaporator. The residue was dissolved in 50 mL of CH_2Cl_2, and washed with a solution of Na_2CO_3 and finally with water. The organic phase was dried (Na_2SO_4) and evaporated to afford the crude product, consisting of a mixture of ethers trans:cis, 3.5:1. The ether (2*S*,6*S*)-**11** was isolated by flash chromatography (hexanes−ethyl acetate, 90:10 → 10:90) and crystallized from hexanes−ethyl acetate, mp 233−234 °C: $[\alpha]_D$ = −96.0° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$; 270 MHz) δ 1.03 (s, 9H), 2.56 (dt, J_1 = 16.5 Hz, J_2 = 2.3 Hz, 1H), 2.74 (s, 3H), 2.90 (dd, J_1 = 16.5 Hz, J_2 = 3.3 Hz, 1H), 5.10 (dd, J_1 = 3.3 Hz, J_2 = 2.3 Hz, 1H), 5.78 (d, *J* = 4.6 Hz, 1H), 7.41−7.56 (m, 5H), 7.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 26.3, 34.1, 41.1, 54.9, 69.1, 86.0, 127.1, 128.5, 130.2, 136.1, 168.9, 174.9.

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64. Found: C, 66.08, H, 7.58.

1-Benzoyl-(2*S*)-isopropyl-3,(5*R*)-dimethylperhydropyrimidin-4-one, (2*S*,5*R*)-13. A solution of diisopropylamine (0.4 mL, 2.9 mmol) in 10 mL of anhydrous THF was cooled to −78 °C before the slow addition of 1.26 mL (2.9 mmol) of *n*-BuLi in hexane (2.3 M). The resulting solution was stirred at −78 °C for 20 min and then treated with 0.759 g (2.9 mmol) of pyrimidinone (*S*)-**4** in 50 mL of THF. The solution formed was stirred at −78 °C for 30 min before the addition of 0.18 mL (2.9 mmol) of methyl iodide. The reaction mixture was stirred at this temperature for 4 h and then treated with 3 mL of saturated ammonium chloride solution. The solvent was evaporated before the addition of 5 mL of water, and the aqueous phase was extracted with three 20-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. Purification of the crude product by flash chromatography (ethyl acetate−hexane, 7:3) afforded 0.601 g (82% yield) of (2*S*,5*R*)-**13**, mp 152−153 °C: $[\alpha]$ = +10.0 (*c* = 1, $CHCl_3$); ^{1}H NMR (DMSO-d_6; 100 °C; 270 MHz) δ 0.94 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H), 2.38 (m, 1H) 2.74 (ddc, *J* = 7.3 Hz, 1H), 2.94 (s, 3H, CH_3N), 3.34 (br s, 1H), 3.79 (dd, J_1 = 12.9 Hz, J_2 = 7.6 Hz, 1H), 5.2 (br s, 1H), 7.42 (m, 5H); ^{13}C NMR (DMSO-d_6; 100 °C; 67.97 MHz) δ 15.1, 18.3, 18.4, 32.4, 33.2, 34.8, 46.7 (br s), 74.2 (br s), 126.3, 128.0, 129.2, 135.3, 169.3, 169.9.

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.03; H, 8.08. Found: C, 70.27; H, 8.05.

***rac-trans*-1-Benzoyl-2-*tert*-butyl-5-hydroxybenzyl-3-methylperhydropyrimidin-4-one, *trans*-15:**



A solution of diisopropylamine (0.31 mL, 2.2 mmol) in 20 mL of anhydrous THF was cooled to −78 °C before the slow addition of 1.2 mL (2.25 mmol) of *n*-BuLi in hexane (1.88 M). The resulting solution was stirred at −78 °C for 30 min and then treated with 0.55 g (2 mmol) of pyrimidinone *rac*-**1** in 20 mL of THF. The solution formed was stirred at −78 °C for 1 h before the addition of 0.31 mL (3 mmol) of benzaldehyde. The reaction mixture was stirred at this temperature for 4 h. The mixture was then treated with 2 mL of saturated ammonium chloride solution. The aqueous phase was extracted with two 50 mL portions of CH_2Cl_2. The combined extracts were washed with a saturated solution of $NaHCO_3$ and then with water, dried (Na_2SO_4), filtered, and evaporated to give the crude product, which was purified by flash chromatography (hexanes−ethyl acetate, 6:4) to afford 0.572 g (75% combined yield) of three stereoisomeric products, in a 58.7:33.9:7.4 ratio. These compounds were separated by flash chromatography and crystallized from hexanes−ethyl acetate.

15a: mp 180−181 °C; ^{1}H NMR ($CDCl_3$; 270 MHz, 50 °C) δ 1.09 (s, 9H), 2.87 (m, 1H), 3.18 (s, 3H), 3.34 (m, 1H), 3.53 (br s, 1H), 4.61 (br s, 1H), 5.80 (br s, 1H), 5.86 (m, 1H), 6.9−7.5 (m, 10H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 27.9, 37.7, 37.9, 39.3, 44.5, 74.2, 74.8, 126.9, 127.1, 127.9, 128.2, 128.5, 130.3, 134.6, 140.2, 170.5, 171.3.

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.54; H, 7.45; N, 7.35.

15b: mp 190−191 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.09 (s, 9H), 2.60 (m, 1H), 3.12 (s, 3H), 3.36 (m, J_1 = 13.9 Hz, J_2 = 8.6 Hz, 1H), 3.87 (m, J_1 = 13.9 Hz, 1H), 4.31 (br s, 1H), 5.54 (m, 1H), 5.85 (br s, 1H), 6.81 (m, 2H), 7.10 (m, 3H), 7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 27.9, 38.1, 38.9, 42.0, 46.3, 73.3, 73.6, 125.4, 126.6, 127.6, 127.9, 128.1, 129.7, 135.5, 141.8, 169.9, 171.1.

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.75; H, 7.43; N, 7.39.

15c: mp 214−215 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.00 (s, 9H), 2.84 (m, 1H), 3.13 (s, 3H), 3.41 (m, 1H), 3.45 (m, 1H), 4.37 (br s, 1H), 5.28 (m, 1H), 5.77 (br s, 1H), 7.1−7.5 (m, 10H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 28.3, 37.1, 37.5, 41.4, 47.6, 71.2, 73.7, 125.7, 126.1, 127.4, 128.3, 128.6, 130.0, 134.5, 140.6, 169.8, 170.3.

***rac*-1-Benzoyl-*r*-2-phenyl-3,*trans*-5-dimethyl-*cis*-6-phenylperhydropyrimidin-4-one, (*r*2-*t*5,*c*6)-20.** A solution of diisopropylamine (0.08 mL, 0.59 mmol) in 20 mL of anhydrous THF was cooled to −78 °C before the slow addition of 0.29 mL (0.59 mmol) of *n*-BuLi in hexane (2.3 M). The resulting solution was stirred at −78 °C for 30 min and then treated with 0.2 g (0.54 mmol) of pyrimidinone *cis*-**8** in 15 mL of THF. The resulting solution was stirred at −78 °C for 50 min before the addition of 0.05 mL (0.8 mmol) of methyl iodide. The reaction mixture was stirred at this temperature for 1 h and at ambient temperature for 5 min. The mixture was treated with 3 mL of saturated ammonium chloride solution and then with 7 mL of water. The aqueous phase was extracted with five 5-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. Purification of the crude product by flash chromatography (hexanes−ethyl acetate, 90:10 → 10:90) and crystallization from CH_2Cl_2−hexane afforded 0.17 g (82% yield) of (*r*2-*t*5,*c*6)-**20**, mp 195−198 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ

Table 4. Crystal Data for All the Structures

	(2*S*)-**1**	**2**	*rac*-**3**	(2*S*)-**4**	(2*S*)-**5**
formula	$C_{16}H_{22}N_2O_2$	$C_{12}H_{14}N_2O_2$	$C_{18}H_{18}N_2O_2$	$C_{15}H_{20}N_2O_2$	$C_{14}H_{18}N_2O_2$
MW	274.36	218.25	294.34	260.33	246.3
cryst system	orthorhombic	monoclinic	tetragonal	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_1/c$	$P4_12_12$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	8.267(2)	13.866(3)	9.210(1)	8.977(2)	6.473(1)
b (Å)	8.332(2)	6.493(1)	9.210(1)	10.907(2)	11.458(2)
c (Å)	22.452(4)	12.323(2)	37.021(7)	14.479(3)	18.147(4)
α (deg)	90	90	90	90	90
β (deg)	90	98.19(3)	90	90	90
γ (deg)	90	90	90	90	90
V (Å^3)	1546.5(6)	1098.1(3)	3140.3(8)	1417.7(5)	1345.9(4)
Z	4	4	8	4	4
D_x (g cm^{-3})	1.18	1.32	1.25	1.22	1.22
F(000)	592	464	1248	560	528
unique reflcns	1906	1025	1936	1423	762
of which $I > 4\sigma$	1647	868	1658	726	677
final *R* value	0.044	0.034	0.034	0.038	0.032

	(2*S*,6*R*)-**6**	*rac*-**7**	*rac*-**8**	(2*S*,6*S*)-**9**	(2*S*,6*S*)-**10**
formula	$C_{17}H_{24}N_2O_2$	$C_{22}H_{26}N_2O_2$	$C_{24}H_{22}N_2O_2$	$C_{16}H_{20}N_2O_4$	$C_{16}H_{20}N_2O_4$
MW	288.38	350.45	370.44	304.34	304.35
cryst system	monoclinic	triclinic	monoclinic	orthorhombic	orthorhombic
space group	$P2_1$	$P\bar{1}$	$P2_1/c$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	7.375(1)	9.250(2)	10.725(2)	7.722(2)	7.548(2)
b (Å)	8.663(2)	10.491(2)	18.053(4)	11.332(2)	10.197(2)
c (Å)	12.807(3)	11.053(2)	10.219(2)	17.745(4)	20.573(5)
α (deg)	90	63.92(3)	90	90	90
β (deg)	90.36(3)	83.50(3)	93.28(3)	90	90
γ (deg)	90	87.49(3)	90	90	90
V (Å^3)	818.3(3)	957.2(3)	1975.3(7)	1552.8(6)	1583.6(6)
Z	2	2	4	4	4
D_x (g cm^{-3})	1.17	1.22	1.25	1.30	1.28
F(000)	312	376	784	648	648
unique reflecns	1551	3351	2800	1585	1886
of which $I > 4\sigma$	929	1740	2108	860	1586 ($>1\sigma$)
final *R* value	0.048	0.043	0.035	0.035	0.037

	(2*S*,6*S*)-**11**	(2*S*,6*S*)-**12**	(2*S*,5*R*)-**13**	(2*S*,5*R*)-**14**	*rac*-**15**
formula	$C_{16}H_{22}N_2O_3$	$C_{17}H_{24}N_2O_2$	$C_{16}H_{22}N_2O_2$	$C_{23}H_{28}N_2O_2$	$C_{22}H_{28}N_2O_3$
MW	290.37	288.38	274.36	364.47	380.49
cryst system	orthorhombic	monoclinic	orthorhombic	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1/c$
a (Å)	6.582(1)	11.458(1)	8.755(2)	10.531(2)	10.278(2)
b (Å)	7.796(1)	5.965(1)	10.799(2)	11.700(2)	18.381(2)
c (Å)	30.965(5)	12.161(2)	15.699(3)	17.020(3)	11.526(2)
α (deg)	90	90	90	90	90
β (deg)	90	104.60(1)	90	90	100.86(1)
γ (deg)	90	90	90	90	90
V (Å^3)	1589.0(3)	804.3(2)	1484.3(5)	2097.1(7)	2138.5(6)
Z	4	2	4	4	4
D_x (g cm^{-3})	1.21	1.19	1.23	1.15	1.18
F(000)	624	312	592	784	816
unique reflecns	2786	3511	1520	2847	3749
of which $I > 4\sigma$	2095 ($>1\sigma$)	2188	772	1891	2766 ($>1\sigma$)
final *R* value	0.047	0.048	0.039	0.045	0.052

	(2*S*,5*R*)-**16**	(2*S*,5*R*)-**17**	*rac*-**18**[a]	*rac*-**19**[a]	*rac*-**20**
formula	$C_{24}H_{30}N_2O_2$	$C_{21}H_{32}N_2O_2$	$C_{16}H_{26}N_2O_2$	$C_{24}H_{30}N_2O_2$	$C_{25}H_{24}N_2O_2$
MW	378.5	344.49	302.42	378.51	384.46
cryst system	monoclinic	monoclinic	orthorhombic	monoclinic	tetragonal
space group	$P2_1$	$P2_1$	*P*bca	$P2_1/c$	$P4_3$
a (Å)	6.084(1)	8.873(2)	20.712	8.311(2)	13.497(2)
b (Å)	11.535(2)	10.616(2)	15.076	22.648(2)	13.497(2)
c (Å)	15.297(3)	11.269(2)	10.807	11.782(3)	11.423(2)
α (deg)	90	90	90	90	90
β (deg)	91.92(3)	108.39(2)	90	105.48(1)	90
γ (deg)	90	90	90	90	90
V (Å^3)	1072.9(3)	1007.3(3)	3374.53	2137.2(8)	2080.9(6)
Z	2	2	8	4	4
D_x (g cm^{-3})	1.17	1.14	1.19	1.18	1.23
F(000)	408	376	1312	816	816
unique reflecns	1987	2475	4894	3146	1981
of which $I > 4\sigma$	1623	1337	1814 ($>3\sigma$)	1978	1802
final *R* value	0.040	0.043	0.049	0.052	0.027

[a] The crystallographic data for compounds **18** and **19** were obtained from the Cambridge Structural Database[34] (compounds JOPZET and JOPZIX, respectively[9a]).

0.82 (d, $J = 6.18$ Hz, 3H), 2.68 (m, 1H), 3.24 (s, 3H), 4.65 (br s, 1H), 6.36 (br s, 1H), 6.90−7.89 (m, 15H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 12.61, 34.80, 40.51, 65.25, 70.86, 125.91, 126.48, 127.29, 127.78, 128.13, 128.32, 128.49, 128.81, 129.74, 136.32, 138.49, 140.20, 171.82, 172.54.

X-ray Analysis. The crystallographic data for compounds **1**−**17** and **20** were collected on Enraf-Nonius-CAD4 diffractometers (in all cases Mo Kα radiation, $\lambda = 0.710\,69$ Å, graphite monochromator). Data reduction for compounds **1**−**9**, **12**−**14**, **16**, **17**, and **20** was achieved with JANA98.[29] The structures were solved by direct methods using the programs SHELXS-97[30] for compounds **1**−**9**, **12**−**14**, **16**, **17**, and **20**, MULTAN80[31] for compound **15**, and MULTAN 11/82[32] for compounds **10** and **11** and refined using SHELXL-97[30] and MoLEN.[33] Space groups, cell constants, number of reflections measured, and final *R* values are collected in Table 4. If not mentioned otherwise, refinement was achieved using reflections with intensity $I > 4\,\sigma(I)$, where the non-H-atoms were refined anisotropically and H-atoms isotropically.

Acknowledgment. We are most grateful to Professors E. L. Eliel (UNC—Chapel Hill), D. Seebach (ETH-Zurich), and D. Cremer (Goeteborg University) for useful comments. We are indebted to the CONACYT (Grant L-0006E) and to the Commission of the European Communities (Contract No. CI1*.0558 ME-JR) for financial support.

Supporting Information Available: Distribution of crystallographic structures containing the 4-cyclohexenone ring in three component diagrams of the conformational space, comparison of experimental and calculated coupling constants of **3** and **4**, conformations of minimum energy for compound **2** found by a stochastic search, crystal packing figures for **9** and **11**, comparison between racemic and enantiopure structures for **1** and **14**, tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths, bond and torsion angles, and anisotropic thermal parameters, and ORTEP figures for **1**−**17** and **20** (108 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

JO991297Q

(29) Vaclav, P. JANA98, A Program for Solved Structures, Praha, 1998.

(30) Sheldrick, G. M. *SHELX97, Programs for Crystal Structure Analysis*, release 97-2; Institute for Inorganic Chemistry der Universität: Tommanstrasse 4, D-3400 Göttingen, Germany, 1998.

(31) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; DeClerq, J. P.; Woolfson, M. M. *MULTAN80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; University of York: York, England, 1980.

(32) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; DeClerq, J. P.; Woolfson, M. M. *MULTAN 11/82, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; University of York: York, England, 1982.

(33) *MoLEN, An Interactive Structure Solution Procedure*; Enraf-Nonius: Delft, The Netherlands, 1990.

(34) Cambridge Crystallographic Data Centre, Cambridge Structural Database System (CSD), 12 Union Road, Cambridge CB2 1EZ, England, April 1997.