Asymmetric Synthesis of β-Amino Acids. 1. Highly Diastereoselective Addition of a Racemic β-Alanine Enolate Derivative to Electrophiles

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β-Alanine, an inexpensive α-amino acid, was converted into the 2-*tert*-butylperhydropyrimidin-4-one derivative **2**, which can be alkylated with high diastereoselectivity via the corresponding enolate. The high stereoselectivity observed for the reaction of **2**-Li with electrophiles seems to be due to steric hindrance generated by an axial disposition of the *tert*-butyl group at C(2), which directs addition from the enolate face opposite to this group. The hydrolysis of the resulting adducts proceeds with 6 N hydrochloric acid to afford α-substituted β-amino acids in good yields. These results pave the road to the development of a new asymmetric synthesis of enantiomerically pure α-substituted β-amino acids.

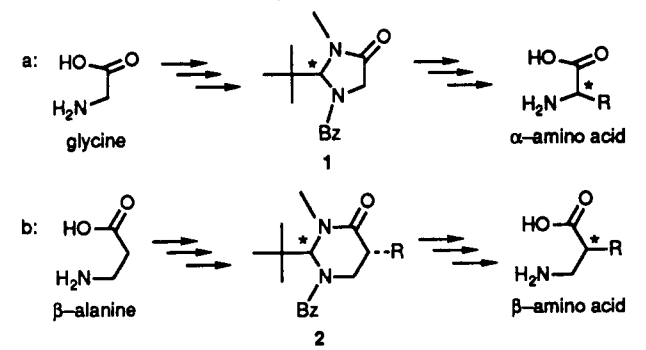
Introduction

As a result of the wide spectrum of applications of α-amino acids, a great deal of interest has been generated in the synthesis of both natural and unnatural amino acids. Nevertheless, the desired amino acids must be synthesized as enantiomerically pure compounds because most amino acids are biologically active in only one enantiomeric form. Indeed, several methods are now available for the preparation of α-amino acids of high enantiomeric purity.[2]

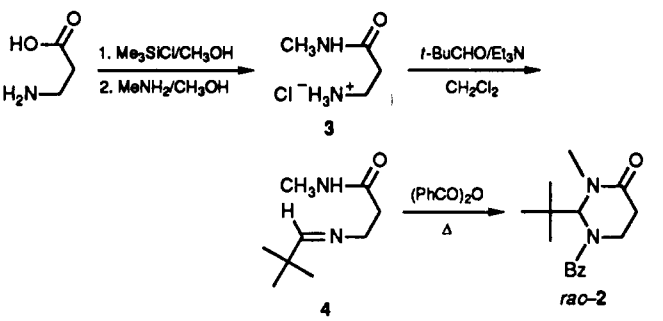
β-Amino acids, although much less abundant than their α analogues, are also present in peptides, and in free form they show interesting pharmacological effects. Furthermore, β-amino acids can be cyclized to β-lactams[3] which are potentially biologically active and of current interest.[4] In this respect, a fair number of methods for the synthesis of racemic β-amino acids have been developed,[5] but very few for the preparation of enantiomerically pure compounds.[6]

Encouraged by the enormous potential of nonracemic derivatives of glycine as precursors of optically active α-amino acids,[7] we decided to explore the usefulness of chiral β-alanine enolates as starting materials for the preparation of (*R*)- or (*S*)-β-amino acids. In particular, in view of the successful development of the imidazolidinone **1** for the preparation of (*R*)- or (*S*)-α-amino acids,[8] it was considered that tetrahydropyrimidinone **2** might serve as an effective reagent for the synthesis of the analogous β-amino acids[9] (Scheme I).

Scheme I



Scheme II



Results and Discussion

A. Synthesis of 1-Benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (2). The heterocycle *rac*-**2** was prepared from β-alanine by initial conversion of its methyl ester to the corresponding *N*-methylamide (**3**), which formed a Schiff base with pivalaldehyde (azeotropic removal of H_2O). Cyclization of imine **4** was possible under

(1) (a) Instituto Politécnico Nacional. (b) ETH-Zürich.

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(3) See, for example: (a) Kim, S.; Chang, P. H. *Tetrahedron Lett.* **1987**, *28*, 2735–2736. (b) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406–2408. (c) Nitta, H.; Hatanaka, M.; Ishimaru, T. *J. Chem. Soc., Chem. Commun.* **1987**, 51–52. (d) Kametani, T.; Huang, S.-P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060–2065. (e) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227–230. (f) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 3593–3596. (g) Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787–3790. (h) Liebeskind, L. S.; Welker, M. E.; Fengl, R. F. *J. Am. Chem. Soc.* **1986**, *108*, 6328–6343. (i) Mkairi, A.; Hamelin, J. *Tetrahedron Ltt.* **1986**, *27*, 4435–4436.

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(9) Although we are aware of the fact that a racemic lithium enolate does not necessarily react with the same selectivity as an enantiomerically pure one, due to aggregate formation (cf. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654), we first sought information about the reactivity of the β-alanine-derived enolate *rac*-**2**-Li prepared by deprotonation of the heterocycle **2**.

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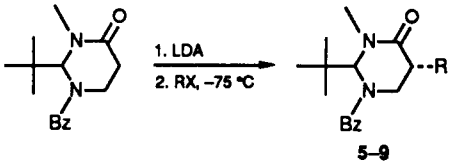
Table I. Diastereoselectivity of Enolate 2-Li Alkylations



5–9

product	RX	ds, %	isolated yield, %	mp, °C
5	CH_3I	96.7	77	98–99
6	$C_6H_5CH_2Br$	95.5	75	144–145
7	*n*-BuI	>96.0	76	89–90
8	n-$C_6H_{13}I$	>96.0	76	49–50
9	CH_2=$CHCH_2Cl$	86.0	78	80–81

severe conditions:[10] treatment with benzoic anhydride and heating to 180 °C for 8 h afforded the desired heterocycle, with an overall yield of 44% (Scheme II).

B. X-ray Diffraction Study of 1-Benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (2). Because of the present interest in the understanding of the precise structure of oxygen- and nitrogen-containing heterocycles,[11] and because such information can be important in ascertaining the factors responsible for the stereoselectivities observed,[12] we carried out an X-ray analysis with a suitable crystal of perhydropyrimidinone **2**.

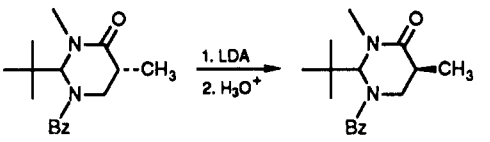
A view of the solid-state structure of **2** is provided in Figure 1 (supplementary material). The pyrimidinone ring is rather flat and has a sofa conformation with five of the six atoms approximately in a plane, and the "acetal" carbon C(2) out of plane.

The most interesting feature of the crystal structure is, however, that the six-membered ring adopts a conformation with an *axial tert-butyl group*! The axial orientation of the bulky substituent could be necessary to maintain conjugation of both ring nitrogens with the carbonyl groups, which would cause stringent steric repulsion with an equatorial *tert*-butyl group at C(2). Six-membered rings bearing axial *tert*-butyl groups are rare,[13] so this finding is of general interest; nevertheless, the practical consequences are also significant; if the enolate would still have a conformation with an axial *tert*-butyl group, one of its faces would be predicted to be sterically hindered for attack by electrophiles. This was indeed the case, as described in the following section.

C. Diastereoselectivity of Alkylation of Enolate 2-Li. The alkylation products **5–9** are formed by treatment of enolate **2**-Li, generated with lithium diisopropylamide (LDA) in THF, with halides RX at −75 °C. High diastereoselectivity (ds = 86–97%) was found as indicated by integration of the ^{13}C NMR spectra of the crude products (Table I).

That addition took place preferentially from the side opposite to the *tert*-butyl group, to afford the trans products, was determined by NMR spectroscopy. In particular, the relatively small coupling constants (J = 4.3 and 6.9 Hz) between H(5) and H(6) are not in line with a product of cis configuration, where one such coupling is expected to be large, $J_{anti} \gtrsim 10$ Hz.

In addition, epimerization at C(5) in adduct **5** was accomplished by enolate formation followed by quenching with aqueous ammonium chloride (eq 1). The ^{13}C NMR



(1)

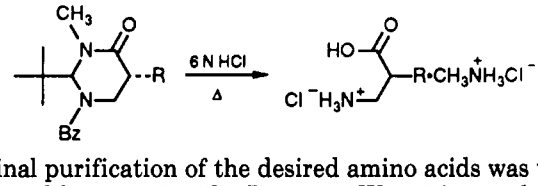
5 *epi*-**5**

signal for the methyl carbon was particularly informative: $\delta(CH_3)$ = 17.32 ppm for the trans product **5**, whereas $\delta(CH_3)$ = 14.63 ppm in *epi*-**5** (this may be due to the upshielding compression effect between the methyl and *tert*-butyl groups; see below).

Finally, an X-ray diffraction study of the benzylated derivative **6** confirmed its relative configuration as trans (Figure 2; supplementary material).

Tables II and III collect the ^1H and ^{13}C NMR data for the perhydropyrimidinones **5–9**.

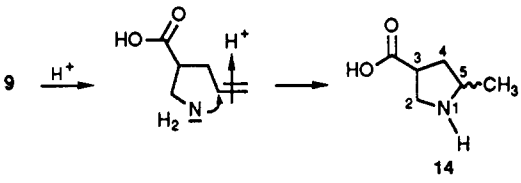
D. Hydrolysis of the Pyrimidinone Adducts 5–9 To Give the α-Substituted β-Amino Acids. The final step of the overall conversions outlined in Scheme I involves the hydrolysis of the heterocyclic products with cleavage of the ring and regeneration of a carboxylic acid. Hydrolysis is best achieved under acidic conditions, which are less likely to cause epimerization at the stereogenic center C(2) of the desired amino acid (important for nonracemic analogues). Nevertheless, drastic conditions were required for the hydrolysis of adducts **5–8** (6 N HCl, 160–180 °C, sealed tube), which proceeded in excellent yields to furnish a mixture of salts of the α-substituted β-amino acids and methylammonium chloride (eq 2).[14]



(2)

Final purification of the desired amino acids was then achieved by use of acidic Dowex 50W × 8 ion-exchange resin. Table IV shows the results of hydrolysis of adducts **5–8**.

With respect to the hydrolysis of the allyl-substituted adduct **9**, the acidic conditions of the hydrolysis provoked a rearrangement of the intermediate β-amino acid, so that the cyclic β-amino acid derivatives *cis*- and *trans*-**14** were isolated instead (eq 3).



(3)

14

Tables V and VI collect the ^1H and ^{13}C NMR data for the β-amino acids obtained in this work (**10–14**).

Conclusions

β-Alanine, an inexpensive and achiral amino acid, was converted efficiently into the racemic *N,N*-acetal **2**.

Unexpectedly, an X-ray crystallographic structure of perhydropyrimidinone **2** revealed the axial orientation of the *tert*-butyl group, which is probably responsible for the high trans diastereoselectivity found in the addition of

(10) Many other protocols failed: Quintana, D. M.Sc. Thesis, Instituto Politécnico Nacional, México, 1989. Estermann, H. Ph.D. Dissertation, ETH-Zurich, 1988.

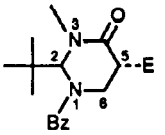
(11) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763–4772 and references therein.

(12) See, for example: Weber, T.; Aeschimann, R.; Maetzke, Th.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365–1377.

(13) (a) Hargrave, K. D.; Eliel, E. L. *Tetrahedron Lett.* **1979**, 1987–1990. (b) Goldsmith, D. J.; Thottathil, J. K. *J. Org. Chem.* **1982**, *47*, 1382–1384 and references therein. (c) See also: Kellie, G. M.; Riddell, F. G. *Top. Stereochem.* **1974**, *8*, 225–269.

(14) The byproducts of hydrolysis, pivalaldehyde and benzoic acid, are easily removed during workup. We observed no elimination of ammonia to the α,β-unsaturated acids under these reaction conditions.

Table II. ^{1}H NMR Data of the Perhydropyrimidinones 5–9 in $CDCl_3$



compd	H(2)	H(5)	$H(6)_a$	$H(6)_b$	$C(CH_3)_3$	NCH_3	aromatics	other
5	5.93	2.65	3.41	3.92	1.20	3.16	7.44	*a*
epi-**5**	5.85	2.54	3.43	3.73	1.15	3.12	7.41	*b*
6	5.94	2.66	3.25	3.68	1.17	3.19	7.42	*c*
7	5.89	2.37	3.63	3.81	1.19	3.13	7.43	*d*
8	5.89	2.32	3.68	3.76	1.18	3.10	7.42	*e*
9	5.94	2.50	3.80	3.80	1.20	3.16	7.63	*f*

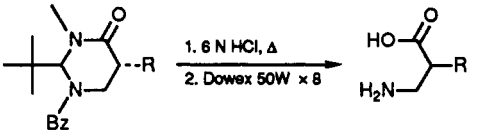
[a] C(5)-CH_3: δ 1.12. [b] C(5)-CH_3: δ 1.23. [c] CH_2Ph: δ 2.34 and 3.70. $CH_2C_6H_5$: δ 7.04. [d] $CH_3(CH_2)_3$: δ 0.74. $CH_3(CH_2)_3$: δ 0.96, 1.33, 1.69. [e] $CH_3(CH_2)_5$: δ 0.95. $CH_3(CH_2)_5$: δ 1.10–1.80. [f] CH_2=$CHCH_2$: δ 4.74, 4.94, 5.64.

Table III. ^{13}C NMR Data (22.49 MHz) of the Perhydropyrimidinones 5–9 in $CDCl_3$

							aromatics						
compd	$C(CH_3)_3$	C(5)	NCH_3	$C(CH_3)_3$	C(6)	C(2)	C_o	C_m	C_p	C_i	NCO	4-CO	other
5	28.00	34.34	37.36	39.12	49.01	74.03	126.49	128.29	129.66	135.07	170.61	171.34	*a*
epi-**5**	28.50	35.44	37.54	38.14	47.94	73.95	126.55	128.72	130.07	135.00	168.97	171.09	*b*
6	28.23	42.08	37.74	39.15	45.00	73.82	126.23	128.62	130.23	134.76	170.01	170.41	*c*
7	28.24	40.09	37.46	39.02	45.65	73.59	126.73	128.44	129.85	135.12	170.52	171.00	*d*
8	28.43	40.33	37.69	39.25	45.83	73.77	126.91	128.67	130.08	135.30	170.75	171.23	*e*
9	28.33	39.49	37.84	39.49	45.59	73.92	127.16	128.57	130.18	134.72	170.36	170.60	*f*

[a] C(5)-CH_3: δ 17.32. [b] C(5)-CH_3: δ 14.63. [c] CH_2Ph: δ 37.46. $CH_2C_6H_5$: δ 127.36, 128.77, 129.85, 138.55. [d] $CH_3(CH_2)_3$: δ 13.62. $CH_3(CH_2)_3$: δ 22.30, 28.83, 31.27. [e] $CH_3(CH_2)_5$: δ 14.04. $CH_3(CH_2)_5$: δ 22.53, 26.87, 29.01, 31.55, 40.32. [f] CH_2=$CHCH_2$: δ 36.32. CH_2=$CHCH_2$: δ 117.80. CH_2=$CHCH_2$: δ 135.06.

Table IV. Hydrolysis of Products 5–8 to the α-Substituted β-Amino Acids 10–13 with 6 N HCl at Ca. 180 °C



starting material	R	product	isolated yield, %	mp, °C
5	CH_3	**10**	69	170–171
6	$PhCH_2$	**11**	66	240–241
7	*n*-Bu	**12**	64	230–231
8	*n*-C_6H_{13}	**13**	62	215–216

enolate **2**-Li to electrophiles. In this way, the chirality center at C(2) induces the stereoselective formation of the new stereogenic center at C(5) of the heterocycle.

The hydrolysis of the resulting adducts proceeds with 6 N hydrochloric acid to afford the desired α-substituted β-amino acids in good yields.

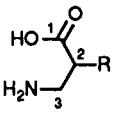
This work sets the basis for the preparation of optically pure α-substituted β-amino acids via enantiomerically pure derivatives of type **2**. The preparation of such starting materials is being actively pursued.

Experimental Section

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[15] The *n*-BuLi employed was titrated according to the method of Juaristi et al.[16]

TLC: Merck-DC-F_{254} plates; detection by UV light. Flash column chromatography:[17] Merck silica gel (0.040–0.063 nm).

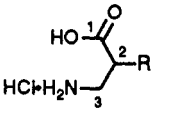
Table V. ^{1}H NMR Data (90 MHz) (ppm) for β-Amino Acids 10–14 in D_2O



compd	R	H(2)	H(3a)	H(3b)	other
10	CH_3	2.67	3.03	3.19	*a*
11	CH_2Ph	2.45	2.47	2.57	*b*
12	*n*-C_4H_9	2.57	3.07	3.20	*c*
13	*n*-C_6H_{13}	2.43	3.05	3.43	*d*
14		*e*			

[a] CH_3: δ 0.90. [b] CH_2Ph: δ 2.40. $CH_2C_6H_5$: δ 7.2. [c] $CH_3(CH_2)_3$: δ 0.87. $CH_3(CH_2)_3$: δ 1.1–1.8. [d] $CH_3(CH_2)_5$: δ 0.96. $CH_3(CH_2)_5$: δ 1.43 (8 H) and 1.80 (2 H). [e] CH_3: δ 0.87. CH_2(4): δ 1.4. H(3): δ 2.37. CH_2(2): δ 2.84. H(5): δ 3.60.

Table VI. ^{13}C NMR Data (22.49 MHz) (ppm) for β-Amino Acids 10–14 in D_2O



compd	R	C(2)	C(3)	CO_2H	other
10	CH_3	40.52	43.61	182.89	*a*
11[e]	CH_2Ph	40.69	45.13	175.26	*b*
12	*n*-C_4H_9	42.31	46.54	182.24	*c*
13	*n*-C_6H_{13}	41.12	43.77	178.40	*d*
14		*f*			

[a] CH_3: δ 16.36. [b] CH_2Ph: δ 36.41. $CH_2C_6H_5$: δ 128.24, 129.92, 130.30, 138.69. [c] $CH_3(CH_2)_3$: δ 14.36. $CH_3(CH_2)_3$: δ 23.13, 29.63, 30.77. [d] $CH_3(CH_2)_5$: δ 14.51. $CH_3(CH_2)_5$: δ 23.04, 26.07, 29.31, 30.39, 31.91. [e] In DMSO-d_6. [f] CH_3: δ 23.40, 23.84. C(4): δ 39.87, 40.20. C(3): δ 42.26, 42.80. C(2): δ 43.50, 44.21. C(5): δ 66.74, 67.28. CO_2H: δ 181.65.

Melting points: Mel-Temp apparatus; not corrected. IR spectra: Nicolet MX-1 FT spectrometer. ^{1}H NMR spectra: Varian EM-390, Varian EM-360, Bruker Spectrospin WM-250, and Bruker Spectrospin WM-300 spectrometers. ^{13}C NMR spectra: JEOL

(15) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975; p 256.
(16) Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603–2606.
(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

FX-90Q (22.49 MHz) spectrometer. Chemical shifts (δ) are given in parts per million downfield from the internal TMS reference; the coupling constants (J) in hertz. MS: Hewlett-Packard 5985-A instrument; m/z values. ds = diastereoselectivity.

Microanalyses were performed by the microanalytical laboratories at ETH-Zürich. The purity of compounds 4 and 11–14, for which elemental analyses are not provided, was judged to be >95%, as evidenced by ^1H and ^{13}C NMR spectra (see supplementary material).

Methyl β-Aminopropionate Hydrochloride. β-Aminopropionic acid (8.9 g, 0.1 mol) in 45 mL of freshly distilled 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 14.0 mL (0.11 mol) of trimethylsilyl chloride (freshly distilled). The reaction mixture was stirred at ambient temperature for 6 h, concentrated to half the original volume in a rotary evaporator, and left standing in a refrigerator for 12 h. The precipitate was then filtered to afford 11.99 g (96% yield) of the desired ester as white crystals with mp 89–90 °C (lit.[18] mp 94–95 °C): ^1H NMR (D_2O, 90 MHz) δ 2.8 (t, J = 5.5 Hz, 2 H), 3.25 (t, J = 5.5 Hz, 2 H), 3.76 (s, 3 H).

***N*-Methyl β-Aminopropionamide Hydrochloride (3).** Methyl β-aminopropionate hydrochloride (10 g, 72 mmol) in 50 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 16 mL (215 mmol) of aqueous 40% methylamine. The resulting mixture was stirred at 0 °C for 8 h and then left standing in a refrigerator overnight. The solvent was evaporated to afford 9.5 g (95% yield) of the desired amide 3 as a semisolid, which was crystallized from methanol; mp 110–112 °C (lit.[19] mp 111–112 °C; ^1H NMR (D_2O, 60 MHz) δ 2.26 (t, J = 6 Hz, 2 H), 2.47 (s, 3 H), 3.00 (t, J = 6 Hz, 2 H); ^{13}C NMR (D_2O, 22.49 MHz) δ 25.89, 38.42, 38.76, 173.23; MS (free amide), m/z 102 (M^+), 73, 58, 44.

β-[*N*-(2′,2′-Dimethylpropylidene)amino]-*N*-methylpropionamide (4). Amide 3 (9.5 g, 69 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 suspension was treated dropwise and with stirring with 19 mL (137 mmol) of freshly distilled Et_3N, and then with 13 mL (117 mmol) of pivalaldehyde. The reaction mixture was heated to reflux for 4 h, with in inverse Dean–Stark trap being used to collect the water that was generated. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to half the original volume, washed with 20 mL of water, dried over anhydrous Na_2SO_4, filtered, and concentrated to afford 6.99 g (60% yield) of the desired imine 4 as a pale-yellow oil: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.08 (s, 9 H), 2.47 (t, J = 6 Hz, 2 H), 2.82 (d, J = 4.5 Hz, 3 H), 3.63 (t, J = 6 Hz, 2 H), 7.1 (br s, 1 H), 7.6 (s, 1 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 25.89, 26.77, 36.08, 37.69, 56.70, 172.55, 173.14; MS, m/z 170 (M^+), 87, 41; HRMS, m/z (M^+) 170.1186 (calcd for $C_9H_{18}N_2O$ 170.1415).

1-Benzoyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (2). Imine 4 (1.48 g, 8.7 mmol) and 1.96 g (9.6 mmol) of benzoic anhydride were heated to 180 °C for 8–9 h. The reaction mixture was allowed to cool to ambient temperature, dissolved in 100 mL of CH_2Cl_2, and washed with 2 N aqueous Na_2CO_3 and then with H_2O. The usual workup procedure afforded a dark oil, which was purified by flash chromatography (*n*-hexane/ethyl acetate, 4:6) to furnish 1.58 g (80% yield) of pure 2: mp 88–89 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 9 H), 2.60 (t, J = 7.5 Hz, 2 H), 3.2 (s, 3 H), 3.85 (m, 2 H), 5.89 (br s, 1 H), 7.45 (s, 5 H); ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 28.12, 29.90, 37.71, 39.28, 41.71, 74.00, 126.66, 128.72, 130.24, 135.17, 168.05, 170.54; IR, 2935, 2901, 1641, 1535 cm^{-1}; MS m/z 274 (M^+), 217, 105, 77, 68.

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.15; H, 8.19; N, 10.25.

General Procedure for the Reaction of Pyrimidinone Enolate (2-Li) with Electrophiles. A solution of $(i\text{-Pr})_2NH$ (154 mg, 1.1 mmol) in 50 mL of THF was cooled down to −75 °C (dry ice/acetone bath) before the slow addition of 0.45 mL (1.1 mmol) of *n*-BuLi in hexane (2.45 M). The resulting solution was stirred at −75 °C for 20 min and then treated with 274 mg (1 mmol) of pyrimidinone 2 in 25 mL of THF. The yellow solution formed was stirred at −75 °C for 1 h before the addition of the electrophile (1.2 mmol), and the reaction mixture was stirred at this temperature for 45 min and at ambient temperature for 30 min. Then the mixture was treated with 10–20 mL of saturated aqueous ammonium chloride. The aqueous phase was separated and extracted three times with 50-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product.

***trans*-1-Benzoyl-2-*tert*-butyl-3,5-dimethylperhydropyrimidin-4-one (5).** The general procedure was followed for the alkylation of 1.1 g (4 mmol) of 2 with 0.3 mL of CH_3I. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 6:4) afforded 0.89 g (77% yield) of 5: mp 98–99 °C; IR 2944, 1659, 1636 cm^{-1}; MS, m/z 288 (M^+), 105, 77; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.63; H, 8.35; N, 9.46.

***cis*-1-Benzoyl-2-*tert*-butyl-3,5-dimethylperhydropyrimidin-4-one (*epi*-5).** The trans isomer (5, 288 mg, 1 mmol) in 25 mL of THF was treated with 0.46 mL of 2.5 M *n*-BuLi at −75 °C. The reaction mixture was stirred at this temperature for 1.5 h and was then quenched with 2 mL of saturated aqueous ammonium chloride. The usual workup procedure afforded crude *epi*-5, which was purified by flash column chromatography (*n*-hexane/ethyl acetate, 6:4) to give 260 mg (90% yield) of the pure product: mp 78–79 °C; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.43; H, 8.30; N, 9.53.

***trans*-1-Benzoyl-5-benzyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (6).** The general procedure was followed for the alkylation of 274 mg (1 mmol) of 2 with 0.16 mL of $C_6H_5CH_2Br$. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 6:4) afforded 273 mg (95% yield) of 6: mp 144–145 °C; IR 2974, 2949, 1646, 1628 cm^{-1}; MS, m/z 364 (M^+), 308, 105, 77; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.81; H, 7.74; N, 7.60.

***trans*-1-Benzoyl-5-*n*-butyl-2-*tert*-butyl-3-methylperhydropyrimidin-4-one (7).** The general procedure was followed for the alkylation of 900 mg (3.3 mmol) of 2 with 0.45 mL of *n*-BuI. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 6:4) afforded 828 mg (67% yield) of 7: mp 89–90 °C; IR 1650, 1630, 1050, 1130 cm^{-1}; MS; m/z 330 (M^+), 273, 105, 77; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.36. Found: C, 72.34; H, 9.14; N, 8.39.

***trans*-1-Benzoyl-2-*tert*-butyl-5-*n*-hexyl-3-methylperhydropyrimidin-4-one (8).** The general procedure was followed for the alkylation of 822 mg (3 mmol) of 2 with 0.49 mL of $n\text{-}C_6H_{13}I$. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 6:4) afforded 806 mg (76% yield) of 8: mp 49–50 °C; IR 1620, 1600, 1140, 1120 cm^{-1}; MS, m/z 358 (M^+), 301, 105, 77; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{22}H_{34}N_2O_2$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.54; H, 9.37; N, 7.51.

***trans*-1-Benzoyl-2-*tert*-butyl-5-(2-propenyl)-3-methylperhydropyrimidin-4-one (9).** The general procedure was followed for the alkylation of 822 mg (3 mmol) of 2 with 0.27 mL (3.3 mmol) of allyl chloride. Purification of the crude product by flash chromatography (*n*-hexane/ethyl acetate, 6:4) afforded 740 mg (78% yield) of 9: mp 80–81 °C; ^1H and ^{13}C NMR data are in Tables II and III, respectively.

Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.47; H, 8.51; N, 8.70.

General Procedure for the Hydrolysis of the Alkylated Pyrimidinones 5–9. A suspension of 1.0 mmol of adduct in 10 mL of 6 N HCl was heated in a sealed ampule to 180 °C for 8 h. The solution was then allowed to cool to ambient temperature and extracted three times with CH_2Cl_2. The aqueous phase was

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evaporated to afford a 1:1 mixture of the amino acid hydrochloride and methylammonium chloride, which was adsorbed to acidic ion-exchange resin Dowex 50W × 8. The resin was washed with distilled H_2O till the washings came out neutral, and then the free amino acid was recovered wtih 1.5 M aqueous NH_3. Evaporation afforded the crystalline amino acid, which was dried under high vacuum at 40 °C.

α-Methyl-β-aminopropionic Acid [(±)-10]. Derivative **5** (576 mg, 2 mmol) was hydrolyzed according to the general procedure to afford 192 mg (69% yield) of pure, free amino acid **10**: mp 170–171 °C (lit.[20] mp 173–174 °C); ^1H and ^{13}C NMR data are in Tables V and VI, respectively; HRMS, m/z (M^+) 103.0607 (calcd for $C_4H_9NO_2$ 103.0633).

Anal. Calcd for $C_4H_9NO_2 \cdot H_2O$: C, 39.66; H, 9.15; N, 11.56. Found: C, 39.44; H, 9.12; N, 11.29.

α-Benzyl-β-aminopropionic Acid [(±)-11]. Derivative **6** (728 mg, 2 mmol) was hydrolyzed according to the general procedure to afford 280 mg (66% yield) of the pure, free amino acid **11**: mp 240–241 °C; ^1H and ^{13}C NMR data are in Tables V and VI, respectively; HRMS, m/z (M^+) 179.0958 (calcd for $C_{10}H_{13}NO_2$ 179.0946).

α-n-Butyl-β-aminopropionic Acid [(±)-12]. Derivative **7** (660 mg, 2 mmol) was hydrolyzed according to the general procedure to afford 232 mg (64% yield) of the pure, free amino acid **12**: mp 230–231 °C; ^1H and ^{13}C NMR data are in Tables V and VI, respectively; HRMS, m/z (M^+) 145.0772 (calcd for $C_7H_{15}NO_2$ 145.1103).

α-n-Hexyl-β-aminopropionic Acid [(±)-13]. Derivative **8** (716 mg, 2 mmol) was hydrolyzed according to the general procedure to afford 258 mg (62% yield) of the pure, free amino acid **13**: mp 215–216 °C; ^1H and ^{13}C NMR data are in Tables V and VI, respectively; HRMS, m/z (M^+) 173.1573 (calcd for $C_9H_{19}NO_2$ 173.1416).

***cis*- and *trans*-3-Carboxy-5-methylpyrrolidines [(±)-14].** Derivative **9** (314 mg, 1 mmol) was hydrolyzed according to the general procedure to afford 158 mg (68% yield) of the pure, free diastereomeric amino acids, *cis*- and *trans*-**14**: mp 140–143 °C; ^1H and ^{13}C NMR data are in Tables V and VI, respectively; HRMS, m/z (M^+) 128.0759 (calcd for $C_6H_{11}NO_2$ 128.0711).

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Supplementary Material Available: Crystal structures for **2** and **6** and ^1H and ^{13}C NMR spectra for **4** and **11–14** (13 pages). Ordering information is given on any current masthead page.

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Synthesis of 1,3-Connected Polyarylmethanes

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1,3-Connected polyarylmethanes were synthesized using repetitive additions of aryllithiums to carbonyl compounds. The polyarylmethanes with molecular mass up to 2900 amu were purified by chromatography and characterized using FABMS, NMR, and elemental analyses. FABMS and 2D COSY NMR were found particularly useful in characterization of large polyarylmethanes.

Introduction

Can ferromagnetism be achieved by preparing an organic solid using large high-spin molecules, which would mimic ferromagnetic domains? Recently, first molecular organometallic ferromagnets and ferrimagnets have been reported;[1-5] however, they are based on small molecules.

Synthesis of strictly organic high-spin (S) molecules mimicking ferromagnetic domains may greatly contribute to understanding of ferromagnetism.[6] Having electronically simple atoms such as carbons as sources of magnetic moments could simplify elucidation of mechanisms for ferromagnetism. Moreover, such organic magnets should possess unique material properties; that is, organics are much different from ceramics or typical metals. Organic molecules with $S > 2$ are rare. The highest spin organic molecule is the $S = 5$ pentacarbene, which consists of five meta-connected benzylidene fragments.[6a] Among polyradicals the highest spin achieved is $S = 2$.[7-9] The theo-

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