over anhydrous $Na_2SO_4$ and evaporated to leave white solid. The solid was dissolved in $CH_2Cl_2$ (8 mL) and MeOH (4 mL), and then Pb $(OAc)_4$ (95 mg, 0.213 mmol, 1.1 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, and 10 drops of 10% HCl was added. The mixture was stirred at room temperature for 1 h and then evaporated. The residue was taken up in EtOAc (10 mL) and $H_2O$ (2 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried and evaporated, leaving white solid, which was separated on PTLC (silica gel, eluted with 18/1 $CH_2Cl_2$/EtOAc) to afford 18 mg of the desired compound as white solid (66.1%), recrystallized from EtOAc/hexanes, mp 105–108 °C, $[\alpha]^{25}_D$ +71.4° (c 2.25, $CH_2Cl_2$). $^1H$ NMR (300 MHz, CDCl): δ TMS 3.26 (s, 3 H), 3.58 (t, 1 H, $J$ = 7.4 Hz), 3.70 (s overlapping with t, 4 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 4.13 (d, 1 H, $J$ = 8.8 Hz), 4.42 (d, 1 H, $J$ = 7.0 Hz), 6.86 (d, 2 H, $J$ = 8.8 Hz), 7.25 (d, 2 H, $J$ = 8.7 Hz). IR (NaCl, neat): 2952, 1746, 1714, 1616, 1518, 1436, 1385, 1344, 1310, 1256, 1200, 1109, 1056, 1030, 951, 935, 835 $cm^{-1}$. Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.10; H, 6.05; N, 3.99. Found: C, 58.04; H, 6.19; N, 3.95.

**(2*S*,3*R*,4*R*,5*R*)-2-Carboxy-3,4-dicarbomethoxy-5-(*p*-nitrophenyl)pyrrolidine (5f).** To (7*R*)-**4f** (68 mg, 0.128 mmol, 1.0 equiv) was added 6 mL of 6 N HCl/MeOH. The resulting mixture was allowed to stir at room temperature for 7 h and then evaporated. The residue was taken up in EtOAc (7 mL) and $H_2O$ (6 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic phase was dried over anhydrous $Na_2SO_4$ and evaporated to afford an oily solid. The solid was dissolved in 4 mL of $CH_2Cl_2$ and 2 mL of MeOH. To the resulting solution was added Pb$(OAc)_4$ (63 mg, 0.141 mmol, 1.1 equiv) at 0 °C, and then the mixture was allowed to stir at 0 °C for 10 min. To the reaction mixture was added 10 drops of 10% aqueous HCl, and the resulting mixture was stirred at rt for 1 h and then evaporated. The residue was taken up in EtOAc (5 mL) and $H_2O$ (4 mL), neutralized with 1 N NaOH to pH = 8, and extracted with EtOAc (5 mL × 3). The combined organic layer was dried over anhydrous $Na_2SO_4$, evaporated and separated on PTLC (silica gel, eluted with 2/1 hexanes/EtOAc) to yield 26 mg of white solid (56%), which was recrystallized from EtOAc/hexanes. Mp: 197.5–198 °C. $[\alpha]^{25}_D$ = +138.5° (c 0.13, $CH_2Cl_2$). $^1H$ NMR (300 MHz, $CDCl_3$): δ TMS 3.28 (s, 3 H), 3.67 (t, 1 H, $J$ = 7.0 Hz), 3.70 (s, 3 H), 3.77 (t, 1 H, $J$ = 8.4 Hz), 3.81 (s, 3 H), 4.20 (d, 1 H, $J$ = 8.8 Hz), 4.58 (d, 1 H, $J$ = 6.8 Hz), 7.58 (d, 2 H, $J$ = 8.6 Hz), 8.21 (d, 2 H, $J$ = 8.8 Hz). IR (NaCl, neat) 2960, 1746, 1710, 1558, 1540, 1515, 1436, 1350, 1309, 1266, 1178, 1115, 1058, 954, 934, 861, 773 $cm^{-1}$. Anal. Calcd for $C_{16}H_{18}N_2O_8$: C, 52.44; H, 4.96; N, 7.65. Found: C, 52.22; H, 5.13; N, 7.65.

**(2*S*,3*R*,4*R*,5*R*)-2-Carboxy-3,4-dicarbomethoxy-5-(tetrahydrofuranyl)pyrrolidine (8).** To a solution of (7*R*)-**4g** (90 mg, 0.189 mmol, 1.0 equiv) in 11 mL of ethanol and 2 mL of THF was added $PdCl_2$ (17 mg, 0.0959 mmol, 0.51 equiv). The resulting mixture was hydrogenated at 60 psi of $H_2$ at room temperature for 72 h, purged with $N_2$, filtered through Celite, and evaporated to leave an oil. The oil was washed with hexanes and $Et_2O$ and triturated with $Et_2O$ to yield a white solid, 62.9 mg (99%). The solid was purified by dissolving in water, and filtering through a $C_{18}$ cartridge (Millipore, Seppak), and then evaporated in vacuo to give a white powder. Mp: 191–193.5 °C. $[\alpha]^{25}_D$ +32° (c 0.15, $CH_3OH$). $^1H$ NMR (270 MHz, $D_2O$): δ HOD 1.84–2.05 (m, 4 H), 3.62 (s, 3 H), 3.65 (m, 4 H), 3.76–3.86 (m, 2 H), 4.17–4.30 (m, 2 H), 4.43 (d, 1 H, $J$ = 6.4 Hz), 4.48 (d, 1 H, $J$ = 6.4 Hz). IR (NaCl, neat): 3300, 2948, 2468, 1738, 1729, 1605, 1271, 970 $cm^{-1}$.

**Acknowledgment.** We are indepted to the National Science Foundation (CHE 8717017), the National Institutes of Health (GM 40988), Symphony Pharmaceutical Co., Merck, Sharp & Dohme Research Laboratories, and Hoffman-La Roche, Inc., for providing financial support.

**Supplementary Material Available:** Atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, hydrogen coordinates, thermal parameters, and ORTEP stereostructures for **4a** and **4d** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# Diastereoselective Alkylation of (3*S*)- and (3*R*)-3-Methylpiperazine-2,5-dione Derivatives. A Convenient Approach to Both (*S*)- and (*R*)-Alanine

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*Received January 23, 1992 (Revised Manuscript Received June 8, 1992)*

Treatment of (3*S*)-3-methylpiperazine-2,5-dione **6a** with LHDMS followed by alkylation of the corresponding enolate with methyl iodide affords (3*S*,6*S*)-3,6-dimethyl derivative **7** in 98% de. The same reaction sequence carried out on (3*R*)-derivative **6b** leads to a 93:7 diastereomeric mixture of (3*R*,6*R*)-**8a** and (3*R*,6*S*)-**8b**. Cleavage of the heterocyclic ring of **7** and **8a** with 57% HI leads to (*S*)- and (*R*)-alanine, respectively. The configuration at C-3 (of **6a** and **6b**) and at C-6 (of **7** and **8a**) can be assigned on the basis of $^1H$ NMR spectroscopy and conformational analysis performed by MMPMI.

Recently, enantiomerically pure α-amino acids, both proteinogenic and nonproteinogenic, have been the target of a number of synthetic methods. A versatile and useful approach consists of the metalation and subsequent alkylation of bis-lactim ethers to afford, after hydrolysis, amino esters in high ee.[1] An interesting asymmetric synthesis of α-amino acids has also been carried out by means of the highly diastereoselective bromination of a chiral 1,4-oxazin-2-one followed by alkylation with retention of configuration. Subsequent hydrolytic cleavage leads to amino acids in high ee.[2]

As part of a program aimed at the use of piperazine-2,5-diones (containing a chiral group bonded to each of the N-atoms) in asymmetric synthesis, we have devised a new approach to the synthesis of α-amino acids in high optical purity by the alkylation of a chiral enolate anion. Similar

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(1) (a) Schollkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Schollkopf, U. *Topics Curr. Chem.* **1983**, *109*, 65.
(2) Williams, R. M. *Synthesis of Optically Active Aminoacids*; Pergamon Press: London, 1989.

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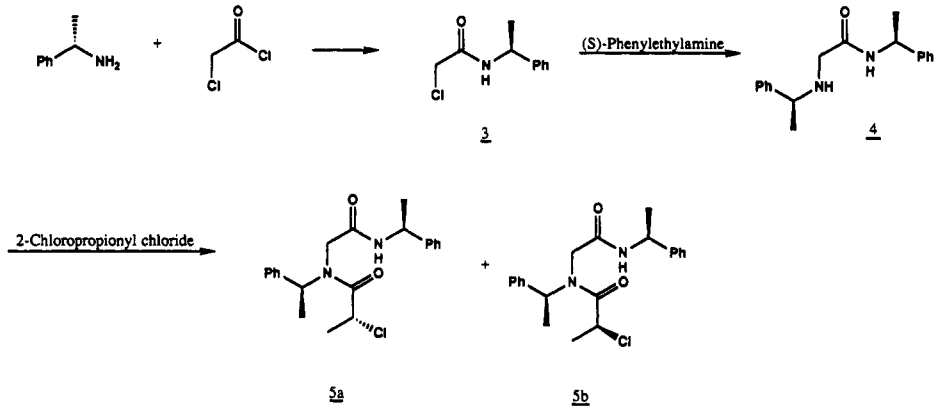
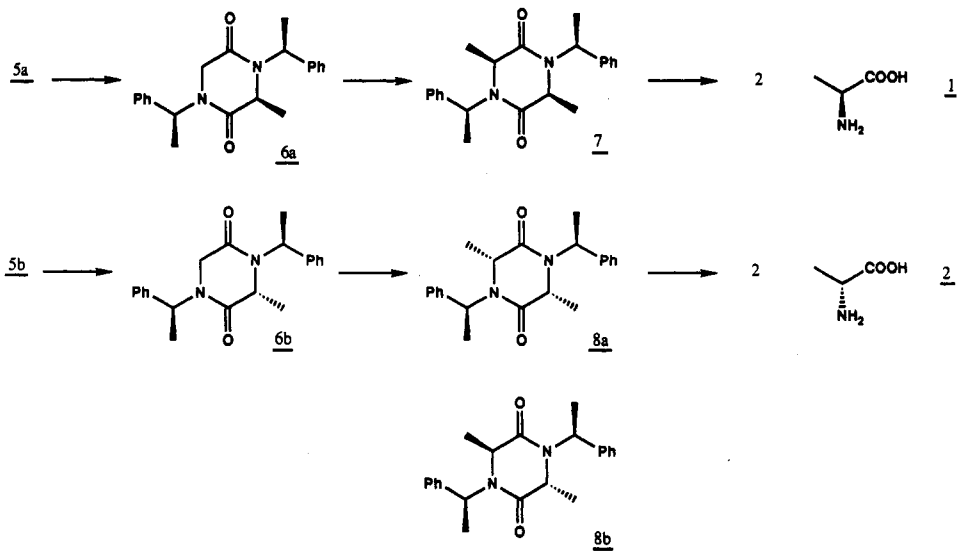
**Scheme I**



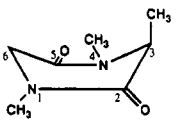

**Scheme II**




approaches to the asymmetric synthesis of amino acids have been reported.[3] The present paper deals with the enantioselective synthesis of (*S*)- and (*R*)-alanine (**1** and **2**) starting from chloroacetyl chloride and (*S*)-phenylethylamine as reported in Schemes I and II.

Chloroacetamide **3** is obtained in 90% yield from the Schotten–Baumann reaction of chloroacetyl chloride with (*S*)-phenylethylamine. Subsequent treatment of **3** with (*S*)-phenylethylamine in dry ethanol at reflux in the presence of anhydrous $K_2CO_3$ leads to glycinamide **4** in 87% yield. Acylation of **4** with (*R,S*)-2-chloropropionyl chloride gives **5a** and **5b** in good yield as a diastereomeric mixture that can be easily separated by silica gel chromatography (or by fractional crystallization from ethyl acetate). The treatment of pure **5a** or **5b** with *n*-BuLi in THF at 0 °C gives diastereomerically pure piperazine-2,5-diones **6a** and **6b**, respectively. Alternatively, the ring closure can be carried out on the diastereomeric mixture of **5a** and **5b** to afford an equimolar amount of **6a** and **6b**. Compounds **6a** and **6b** are easily separated either by silica gel chromatography or by fractional crystallization from ethyl acetate.

When pure **6a** is treated with 1 equiv of LHMDS at 0 °C, the corresponding enolate anion is formed, and subsequent addition of methyl iodide at −78 °C yields alkylation product **7** in very good yield. The electrophile adds cis to the methyl group with high 1,4-asymmetric induction, and the diastereomeric excess is greater than 98%, as determined by $^1$H NMR. Debenzylation and hydrolytic cleavage of the heterocyclic ring are carried out in one step with 57% HI at reflux. After ion-exchange chromatography with Amberlyst H 15 ($H^+$ form), (*S*)-alanine is obtained in 90% yield.



**9**

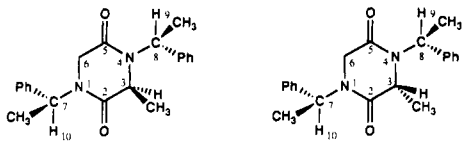
**Figure 1.** Most stable calculated conformation of *N,N'*-dimethyl-3-methylpiperazine-2,5-dione.

The same reaction sequence can be carried out with comparable yields starting from **5b**, although the alkylation of **6b** proceeds with lower 1,4-asymmetric induction, the cis–trans ratio of **8a**:**8b** being 93:7. However, pure *cis*-**8a** can be isolated by silica gel chromatography; subsequent treatment of **8a** with 57% HI and purification by Amberlyst H 15 led to (*R*)-alanine in 90% yield.

The absolute configuration of the stereogenic center C-3 of **6a** and **6b** can be determined on the basis of $^1$H NMR data and full conformational analysis performed by using the MMPMI program,[4] as previously described for similar

(3) Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916 and references cited therein.

(4) Program MMPMI Version 1 (1986) by K. E. Gilbert and J. J. Gajewskyi, Department of Chemistry, Indiana University, Bloomington, IN 47405. The program is an extension of Allinger's MM2 (QCPE-395 and MMP1 (QCPE-318) molecular mechanics programs.



6a 6b

**Figure 2.** Planar projections of isomers (3*S*)-**6a** and (3*R*)-**6b**.

**Table I. Conformational Energies and Relative Abundances of 6a and 6b**

| compd | conformer | $\alpha^a$ | $\beta^b$ | $E^c$ | population$^d$ (%) |
|---|---|---|---|---|---|
| (3*S*)-**6a** | A | −6 | −2 | 0 | 47 |
| | B | −6 | 162 | 0.2 | 33 |
| | C | 164 | 161 | 0.85 | 11 |
| | D | 164 | −2 | 0.95 | 9 |
| (3*R*)-**6b** | E | −8 | −5 | 0 | 37 |
| | F | −4 | 177 | 0.2 | 26 |
| | G | 172 | 177 | 0.35 | 20 |
| | H | 175 | −4 | 0.45 | 17 |

[a] Dihedral angle C-2, N-1, C-7, H-10. [b] Dihedral angle C-5, N-4, C-8, H-9. [c] Relative energy (kcal/mol). [d] Relative abundance as $e(-E/RT)$ for $T$ = 300 K.

molecules.[5] The usefulness and reliability of this approach are confirmed by the optical rotation values of the isolated (*S*)- and (*R*)-alanine, which agree with the literature.

A preliminary investigation carried out on a model compound, *N,N'*-dimethyl-3-methylpiperazine-2,5-dione (**9**), has shown that the minimum energy conformation is a boat conformation in which the methyl group lies in the axial position, away from the carbonyl oxygen. The conformer having the methyl group in the equatorial position is 1.5 kcal/mol less stable (Figure 1). This result agrees with the data obtained for *cis*- and *trans*-3,6-dimethylpiperazine-2,5-dione using a CFF approach.[6]

In the calculated geometry of **6a** and **6b** N-1, C-2, N-4, and C-5 are almost coplanar, while C-3 and C-6 are out of the plane. The dihedral angle between N-1, C-2, C-3, and N-4 is about 38 °C. A complete conformational analysis of diastereomers **6a** and **6b** has been accomplished by the flipping of the heterocyclic ring and a full rotation around both the N-1–C-7 and N-4–C-8 bonds (see Figure 2).

In the geometries of both (3*S*)-**6a** and (3*R*)-**6b** corresponding to the energetic minima, the (C-3)-$CH_3$ preferentially lies in an axial position rather than in an equatorial one, in analogy to model compound **9** previously described. In fact, the conformations of **6a** and **6b** having the methyl in an axial arrangement are 1.95 and 1.85 kcal/mol more stable, respectively.

This calculated geometry agrees with the results of NOE experiments on **6a** and **6b**. Irradiation of the (C-3)-$CH_3$ of (3*S*)-**6a** causes a 5% NOE on the (C-6)-H (δ 3.92) and a 7% NOE on the (C-3)-H. Irradiation of the (C-3)-$CH_3$ of (3*R*)-**6b** causes a 7% NOE on the (C-6)-H (δ 3.33) and 17% NOE on the (C-3)-H. These results can be rationalized by assuming that **6a** and **6b** are in a boat conformation in which the axial (C-3)-$CH_3$ eclipses the (C-6)-H (Figure 3).

In all of the conformations corresponding to the more populated minima, the benzylic hydrogens and the carbonyl group are either almost synperiplanar or almost antiperiplanar (see Table I). In Figure 4, the two more populated conformers of (3*S*)-**6a** and (3*R*)-**6b** are conveniently described by Newman projection along the N-4–C-8 bond.

**Table II. Selected Chemical Shifts (δ) for (3*S*)-6a and (3*R*)-6b**

| compd | (C-3)-$CH_3$ | (C-3)-H |
|---|---|---|
| (3*S*)-**6a** | 1.51 (d) | 3.82 (q) |
| (3*R*)-**6b** | 0.71 (d) | 4.04 (q) |

**Table III. Selected Chemical Shifts (δ) for (3*S*,6*S*)-7 and (3*R*,6*R*)-8a**

| compd | (C-3)-$CH_3$ (C-6)-$CH_3$ | (C-3)-H (C-6)-H |
|---|---|---|
| (3*S*,6*S*)-**7** | 1.58 (d) | 3.82 (q) |
| (3*R*,6*R*)-**8a** | 0.87 (d) | 4.09 (q) |

The selected $^1$H-NMR chemical shifts reported in Table II show that the (C-3)-$CH_3$ absorbs at higher field (δ 0.71) in (3*R*)-**6b** than in (3*S*)-**6a** (δ 1.51). In contrast, the (C-3)-H in (3*S*)-**6a** is shifted upfield by 0.22 ppm with respect to that of (3*R*)-**6b**. These chemical shift values can be explained by means of the phenyl shielding effect that occurs in the more stable calculated conformations (see Figure 4). The (C-3)-$CH_3$ is more shielded in (3*R*)-**6b**, in which the methyl group is eclipsed by the phenyl group, than in (3*S*)-**6a**, while the (C-3)-H experiences a greater shielding in (3*S*)-**6a** than in (3*R*)-**6b**.

The shielding effects can only take place in the conformations in which the benzylic hydrogen lies synperiplanar to the carbonyl group (see A and E in Figure 4). Therefore, the upfield shifts of (C-3)-H and (C-3)-$CH_3$ in (3*S*)-**6a** and (3*R*)-**6b**, respectively, are a result of the average phenyl shielding contribution of the more populated conformers. It is important to note that no shielding effect appears in the rotamers having the benzylic hydrogen antiperiplanar (see B and F in Figure 4). Thus, these rotamers are not useful to explain the above-mentioned chemical shift values.

On the basis of the $^1$H-NMR analysis, we have also established the absolute configuration of stereogenic center C-6 in diastereomers **7**, **8a**, and **8b**. In the $^1$H-NMR spectrum of **7**, the signals for (C-3)-$CH_3$ and (C-6)-$CH_3$ overlap (δ 1.58), as do the signals for (C-3)-H and (C-6)-H (δ 3.82) (Table III), thus showing their magnetic equivalence. Analogously, the $^1$H-NMR spectrum of **8a** shows the magnetic equivalence of the methyl groups at C-3 and C-6 (δ 0.87) and the protons at C-3 and C-6 (δ 4.09) (Table III). From the $^1$H-NMR spectrum of **7**, in which (C-6)-$CH_3$ and (C-6)-H have the same chemical shifts as (C-3)-$CH_3$ and (C-3)-H, respectively, of **6a**, it is possible to infer the (*S*)-configuration of C-6 for diastereomer **7**. The (*R*)-configuration at C-6 in **8a** can be analogously deduced from the similarity of the chemical shifts of (C-6)-$CH_3$ and (C-6)-H in **8a** to those of (C-3)-$CH_3$ and (C-3)-H, respectively, in **6b** (Tables II and III).

It is interesting to note that in the more stable conformations of both **7** and **8a** the C-3 and C-6 methyls are in a cis-diaxial arrangement. Molecular modeling showed the diaxial conformations of **7** and **8a** to be 1.7 and 1.5 kcal/mol, respectively, more stable than the cis-diequatorial conformers.

Finally, the absolute configuration of stereogenic center C-6 in **8b** has been assigned by a comparative analysis of the $^1$H-NMR spectra of **7**, **8a**, and **8b**. In addition, the correct assignment has been confirmed by a positive NOE (6%) observed on the (C-6)-H (δ 3.9) when the (C-3)-$CH_3$ (δ 1.1) was irradiated. (A 10% NOE was observed on the (C-3)-H.) These NOEs confirm the trans relationship of the $CH_3$ groups in the heterocyclic ring.

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(6) Karplus, S.; Lifson, S. *Biopolymers* **1971**, *10*, 1973.

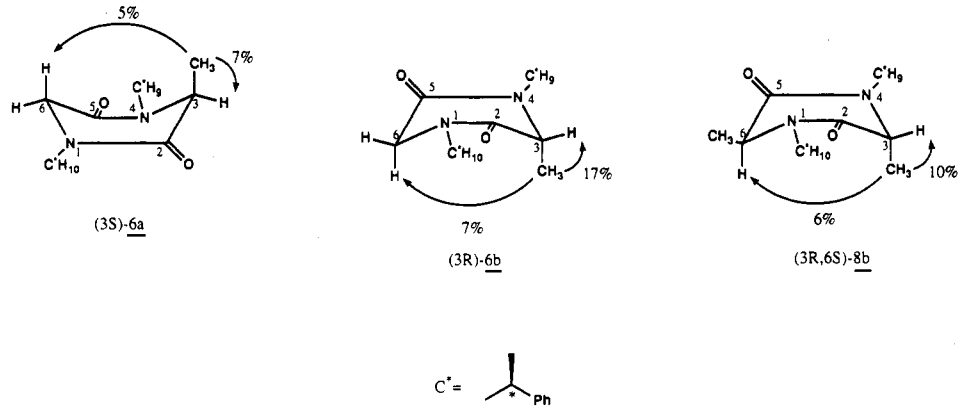


**Figure 3.** NOEs observed on isomers (3*S*)-**6a**, (3*R*)-**6b**, and (3*R*,6*S*)-**8b**.

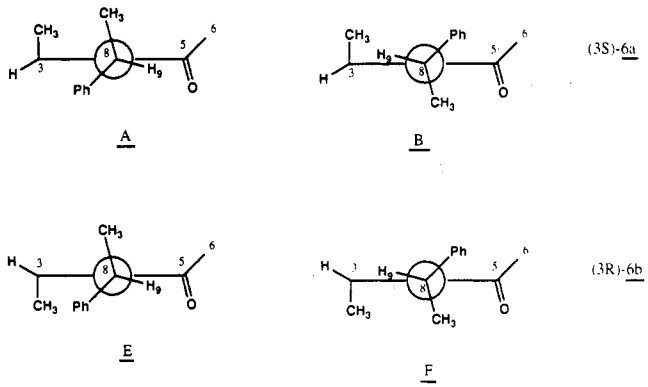


**Figure 4.** Newman projections (along N-4–C-8 bond) of conformers A,B and E,F related to isomers (3*S*)-**6a** and (3*R*)-**6b**, respectively (see Table I).

Other alkylating reagents are being investigated to determine whether the high cis-1,4-induction described in this paper falls in a general trend. Further investigations are in progress to explain this stereochemical outcome which is opposite to that observed by Sholkopf in the bis-lactim ether alkylation.[1]

## Experimental Section

Melting points are uncorrected. Magnetic resonance spectra were recorded at 300 MHz with $CDCl_3$ as a solvent, unless otherwise stated. Optical rotation values were recorded on a Perkin-Elmer 541 polarimeter. THF was distilled from LAH or sodium benzophenone immediately prior to use. All reactions involving organometallic reagents were carried out under an argon atmosphere.

**(*S*)-*N*-(1-Phenyleth-1-yl)chloroacetamide (3).** To a solution of (*S*)-1-phenylethylamine (23 mL, 0.180 mol) and $Na_2CO_3 \cdot 10H_2O$ (27 g) in water–acetone (1:1, 200 mL), at 0 °C, was slowly added chloroacetyl chloride (14.5 mL, 0.180 mol) dissolved in acetone (50 mL) dropwise. After 1 h, the solvent was removed under reduced pressure, and the residue was acidified with 6 M HCl. After extraction with ethyl acetate and removal of the solvent, **3** was obtained as a solid (32 g, 90% yield), which can be crystallized from ethyl acetate/ether (mp 94 °C); IR (Nujol) 3260, 1650 $cm^{-1}$; $^1H$ NMR $\delta$ 1.55 (d, 3 H, $J$ = 7.2 Hz), 4.05 (dd, 2 H, $J$ = 15.2 Hz), 5.15 (m, 1 H), 6.80 (bs, 1 H, NH), 7.35 (m, 5 ArH); $^{13}C$ NMR $\delta$ 21.8, 42.8, 49.5, 126.6, 128.1, 129.3, 142.9, 165.7; $[\alpha]_D$ –57.5° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12. Found: C, 60.84; H, 6.11.

**(4*S*)-*N*-((*S*)-1-Phenyleth-1-yl)-4-phenyl-3-azapentanamide (4).** To a solution of **1** (22.85 g, 0.116 mol) and (*S*)-1-phenylethylamine (15 mL, 0.116 mol) in absolute ethanol (100 mL) was added $K_2CO_3$ (8.24 g), and the mixture was refluxed for 8 h. The solvent was removed in vacuo, water was added, and the mixture was extracted with ethyl acetate. After the extract was dried, the solvent was removed, and the residue was recrystallized from ether. The product was obtained pure in 87% yield: mp 70 °C; IR (Nujol) 3340, 1630 $cm^{-1}$; $^1H$ NMR $\delta$ 1.35 (d, 3 H, $J$ = 7.2 Hz), 1.45 (d, 3 H, $J$ = 7.2 Hz), 1.8 (s, 2 H), 3.2 (m, 2 H), 3.7 (q, 1 H, $J$ = 7.2 Hz), 5.1 (m, 1 H), 7.30 (m, 10 ArH); $^{13}C$ NMR $\delta$ 21.8, 23.6, 48.0, 50.6, 58.5, 126.2, 126.7, 127.4, 127.5, 127.7, 128.7, 128.8, 143.6, 144.6, 171.1; $[\alpha]_D$ –68.5° (*c* 2, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85. Found: C, 76.41; H, 7.87.

**(4*S*)-*N*-((*S*)-1-Phenyleth-1-yl)-4-phenyl-3-((2*S*,*R*)-2-chloropropion-1-yl)-3-azapentanamide (5a and 5b).** To a solution of **2** (36.66 g, 0.130 mol) in water–acetone (1:1, 200 mL) at 0 °C was added $Na_2CO_3 \cdot 10H_2O$ (20.0 g). Then (*R*,*S*)-2-chloropropionyl chloride (13 mL; 0.130 mol) in acetone (50 mL) at 0 °C was slowly added dropwise. After 1 h, the solvent was removed under reduced pressure, and the residue was acidified with 6 M HCl. After extraction with ethyl acetate and removal of the solvent, **5a** and **5b** (43.4 g, 90% yield) were separated by silica gel chromatography with 85:15 cyclohexane–ethyl acetate. (Alternatively, it was possible to crystallize diastereomer **5b** from ethyl acetate.)

**5a**: $R_f$ = 0.46 (cyclohexane–ethyl acetate (1:1)); white solid; mp 112 °C; $^1H$ NMR (DMSO, 70 °C) $\delta$ 1.25 (d, 3 H, $J$ = 7.1 Hz), 1.35 (d, 3 H, $J$ = 7.1 Hz), 1.60 (d, 3 H, $J$ = 6.4 Hz), 3.90 (dd, 2 H, $J_{AB}$ = 17 Hz), 4.80 (q, 1 H, $J$ = 7.1 Hz), 4.90 (q, 1 H, $J$ = 7.1 Hz), 5.75 (q, 1 H, $J$ = 6.4 Hz), 7.30 (m, 10 ArH); $[\alpha]_D$ –152.6° (*c* 0.95, $CHCl_3$).

**5b**: $R_f$ = 0.26 (cyclohexane–ethyl acetate (1:1)); white solid; mp 134 °C; $^1H$ NMR (as a 1:1 mixture of conformers) $\delta$ 1.10 (d, 3 H, $J$ = 7.1 Hz), 1.35 (d, 3 H, $J$ = 7.1 Hz), 1.40 (d, 3 H, $J$ = 7.1 Hz), 1.65 (d, 3 H, $J$ = 7.1 Hz), 1.75 (d, 3 H, $J$ = 7.1 Hz), 3.7 (dd, 2 H, $J_{AB}$ = 17 Hz), 3.85 (dd, 2 H, $J_{AB}$ = 7 Hz), 4.60 (q, 1 H, $J$ = 7.1 Hz), 4.70 (m, 1 H, $J$ = 7.1 Hz), 4.80 (q, 1 H, $J$ = 7.1 Hz), 4.90 (m, 1 H, $J$ = 7.1 Hz), 5.40 (q, 1 H, $J$ = 7.1 Hz), 5.50 (d, 1 H, $J$ = 7.1 Hz), 6.10 (q, 1 H, $J$ = 7.1 Hz), 6.50 (d, 1 H, $J$ = 7.1 Hz), 7.30 (m, 10 ArH); $[\alpha]_D$ –96.5° (*c* 0.95, $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_2Cl$: C, 67.82; H, 6.51. Found: C, 67.69; H, 6.49.

**(3*S*)-1,4-*N*,*N*-((*S*)-1-Phenyleth-1-yl)-3-methylpiperazine-2,5-dione (6a).** To a solution of **5a** (21.2 g, 57 mmol) in dry THF (200 mL) at 0 °C, under an inert atmosphere, was added *n*-BuLi (23 mL of 2.5M solution in hexane, 57.5 mmol). After 2 h, the cooling bath was removed, 2 M HCl was added, and the mixture was extracted with ethyl acetate. After the extract was dried and the solvent was removed, the residue was purified by silica gel chromatography (hexane–ethyl acetate (80:20)) to give **6a**, as an oil, which slowly crystallizes as a white solid (17.6 g, 92% yield); mp 110 °C; IR (Nujol) 1660 $cm^{-1}$; $^1H$ NMR $\delta$ 1.51 (d, 3 H, $J$ = 7.2 Hz), 1.52 (d, 3 H, $J$ = 7.2 Hz), 1.62 (d, 3 H, $J$ = 7.2 Hz), 3.62 (d, 1 H, $J$ = 16.8 Hz), 3.82 (q, 1 H, $J$ = 7.2 Hz), 3.92 (d, 1 H, $J$ = 16.8 Hz), 5.83 (q, 1 H, $J$ = 7.2 Hz), 5.85 (q, 1 H, $J$ = 7.2 Hz), 7.30 (m, 10 ArH); $^{13}C$ NMR $\delta$ 15.3, 17.3, 19.6, 44.5, 49.9, 51.4, 53.0, 126.9, 126.95, 128.0, 128.05, 128.8, 128.85, 138.7, 139.2, 165.0, 167.9; $[\alpha]_D$ –263.4° (*c* 2.01; $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19. Found: C, 75.06; H, 7.17.

**(3*R*)-1,4-*N*,*N*-((*S*)-1-Phenyleth-1-yl)-3-methylpiperazine-2,5-dione (6b).** Compound **6b** was prepared from **5b** by the procedure described for **6a**. The product crystallized from ethyl acetate as a white solid (17.2 g, 90% yield), mp 123 °C; IR (Nujol) 1660 $cm^{-1}$; $^1H$ NMR $\delta$ 0.71 (d, 3 H, $J$ = 7.2 Hz), 1.56 (d, 3 H, $J$ = 7.1 Hz), 1.58 (d, 3 H, $J$ = 7.1 Hz), 3.33 (d, 1 H, $J$ = 17 Hz), 3.67 (d, 1 H, $J$ = 17 Hz), 4.04 (q, 1 H, $J$ = 7.2 Hz),

5.90 (q, 1 H, $J$ = 7.1 Hz), 5.93 (q, 1 H, $J$ = 7.1 Hz), 7.30 (m, 10 ArH); $^{13}$C NMR $\delta$ 15.0, 15.8, 17.7, 44.8, 49.9, 50.5, 52.7, 126.9, 127.8, 128.0, 128.3, 128.5, 128.6, 138.3, 139.1, 164.4, 167.8; $[\alpha]_D$ −366.4° ($c$ 2, $CHCl_3$).

**(3*S*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenyleth-1-yl)-3,6-dimethylpiperazine-2,5-dione (7).** LHMDS (20 mL of 1 M solution in THF, 20 mmol) was slowly added to a solution of **6a** (6.72 g, 20 mmol) in dry THF (60 mL) at 0 °C. After 2 h, the reaction mixture was cooled to −78 °C and methyl iodide (2.84 g, 20 mmol) in dry THF (20 mL) was added. After 2 h, 2 M HCl (10 mL) was added, and the mixture was extracted with ethyl acetate. After the extract was dried and the solvent was removed, the residue was purified by silica gel chromatography to give 7 as a white solid (6.4 g, 92% yield); mp 185 °C; IR (Nujol) 1660; $^1$H NMR $\delta$ 1.58 (d, 6 H, $J$ = 7.1 Hz), 1.62 (d, 6 H, $J$ = 7.1 Hz), 3.82 (q, 2 H, $J$ = 7.1 Hz), 5.8 (q, 2 H, $J$ = 7.1 Hz), 7.25 (m, 10ArH); $^{13}$C NMR $\delta$ 17.2, 21.7; 51.3, 52.6, 126.7, 127.6, 128.4, 138.6, 167.8; $[\alpha]_D$ −232.4° ($c$ 2.16, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 7.48. Found: C, 75.5; H, 7.46.

**(3*R*,6*R*)-1,4-*N*,*N*-((*S*)-1-Phenyleth-1-yl)-3,6-dimethylpiperazine-2,5-dione (8a) and (3*R*,6*S*)-1,4-*N*,*N*-((*S*)-1-Phenyleth-1-yl)-3,6-dimethylpiperazine-2,5-dione (8b).** Starting from **6b**, the alkylation reaction was performed as described for **6a**. A mixture of **8a** and **8b** was obtained in 90% yield and a diastereomeric ratio of 90:10. Diastereomers **8a** and **8b** were separated by silica gel chromatography (cyclohexane–ethyl acetate (85:15)). Isomer **8a**: white solid; mp 175 °C; $^1$H NMR $\delta$ 0.87 (d, 6 H, $J$ = 7.1 Hz), 1.58 (d, 6 H, $J$ = 7.1 Hz), 4.09 (q, 2 H, $J$ = 7.1 Hz), 5.85 (q, 2 H, $J$ = 7.1 Hz), 7.3 (m, 10 ArH); $^{13}$C NMR $\delta$ 15.6, 20.2, 50.9, 53.0, 127.5, 127.7, 128.3, 139.4, 167.5; $[\alpha]_D$ −316.9° ($c$ 2.04, $CHCl_3$). Isomer **8b**: $^1$H NMR $\delta$ 1.1 (d, 3 H, $J$ = 7.1 Hz), 1.45 (d, 3 H, $J$ = 7.1 Hz), 1.65 (d, 3 H, $J$ = 7.1), 1.7 (d, 3 H, $J$ = 7.1 Hz), 3.9 (q, 1 H, $J$ = 7.1 Hz), 4.20 (q, 1 H, $J$ = 7.1 Hz), 5.8 (q, 1 H, $J$ = 7.1 Hz), 5.85 (q, 1 H, $J$ = 7.1 Hz), 7.30 (m, 10ArH). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.4; H, 7.48. Found: C, 75.4; H, 7.45.

**(*S*)-Alanine (1).** To 10 mL of 57% hydriodic acid was added 7 (1.1 g, 3 mmol), and the mixture was refluxed for 1 h. Then the resulting solution was extracted with ethyl acetate, and the aqueous solution was evaporated under reduced pressure. The residue was dissolved in water (10 mL) and adsorbed on ion-exchange resin Amberlyst H 15. The resin was washed with distilled water and then eluted with 5 M $NH_4OH$ to give (*S*)-alanine (0.48 g, 90% yield). $^1$H NMR ($D_2O$, DCl) $\delta$ 1.50 (d, 3 H, $J$ = 7 Hz), 3.8 (q, 1 H, $J$ = 7 Hz); $[\alpha]_D$ +14.5° ($c$ 1, 5 M HCl) (lit.[7] $[\alpha]_D$ +14.6 (5 M HCl)).

**(*R*)-Alanine (2).** The product was obtained in 90% yield starting from **8a** and following the procedure described for (*S*)-alanine (1): $[\alpha]_D$ −14.45° ($c$ 1, 5 M HCl) (lit.[7] $[\alpha]_D$ +14.6° (5 M HCl) for the (*S*)-isomer).

**Acknowledgment.** We thank MURST (Rome) for financial support.

**Registry No.** 1, 56-41-7; 2, 338-69-2; 3, 36293-01-3; 4, 143746-58-1; 5a, 143746-59-2; 5b, 143837-97-2; 6a, 143746-62-7; 6b, 143837-99-4; 7, 143746-60-5; 8a, 143746-61-6; 8b, 143837-98-3; (*S*)-$PhCHMeNH_2$, 2627-86-3; $ClCH_2COCl$, 79-04-9; (±)-$H_3CCHClCOCl$, 76248-57-2.

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# A Conformational Study of [3.3]Metacyclophanes through Variable-Temperature $^1$H NMR and Optical Rotation[1]

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*Received February 20, 1992*

Conformational behavior of 2,2,11,11-tetradeuterio[3.3]metacyclophanes 1-$d_4$ and 2-$d_4$ has been studied by a variable-temperature (VT) $^1$H NMR method. In order to simplify the interpretation of the $^1$H NMR spectrum, four deuteriums were introduced at C-2 and C-11 positions of the trimethylene bridges of [3.3]metacyclophanes by reductive desulfurization of 2,11-bis(1,4-dithiabutane-1,4-diyl)[3.3]metacyclophanes 4 and 5 with tri-*n*-butyltin deuteride. Our previous conformational study of tetradeuterio-1,4-dioxa[4.3.3]cyclophane (3-$d_4$) revealed that the temperature-dependent phenomenon in the $^1$H NMR spectrum of 1 was ascribed to the inversion the trimethylene bridges. The work also suggested the presence of benzene ring inversion. To confirm this, optically active [3.3]metacyclophanechromium tricarbonyl complexes (−)- and (+)-17 were prepared by means of the HPLC separation of racemic complex (±)-17 using a chiral stationary phase. Racemization occurred when (−)- and (+)-17 were decomplexed at 20 °C. This result as well as the fact that the energy barrier ($\Delta G^*$) for the benzene ring inversion could not be detected by the VT NMR method indicated that the barrier is much lower than that of trimethylene bridge inversion ($\Delta G^*$ = 11–12 kcal/mol). The most stable conformer of 1-$d_4$ and 2-$d_4$ is a syn-(chair-chair), and the less stable conformer is estimated to be a syn(chair-boat) on the basis of the $^1$H NMR data.

## Introduction

[*m.n*]Metacyclophanes can generally adopt two different geometries, syn and anti.[5] Lehner et al. reported that the conformation of [*m.n*]metacyclophane in solution is sensitive both to chain length of the bridges and substitution. Thus [3.3]metacyclophane ($m$ = $n$ = 3, 1) preferentially adopts the syn geometry, but its lower and higher homologs ($m$ = 2–4; $n$ = 2,3) adopt the anti geometry.[6] Recently,

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(1) Conformational analysis of [3.3]cyclophanes, Part 4. This paper is taken in part from the Ph.D. Dissertation of K. Sako. For previous papers, see refs 2 (part 1), 3 (part 2), and 4 (part 3).

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0022-3263/92/1957-6536$03.00/0 