Biomimetic Synthesis of Chapliatrin Type Compounds

Antonio G. González,* Antonio Galindo, Horacio Mansilla, Angeles Gutiérrez, and José A. Palenzuela

Instituto Universitario de Química Orgánica, Universidad de La Laguna—Instituto de Productos Naturales Orgánicos, CSIC, La Laguna, Tenerife, Canary Islands, Spain

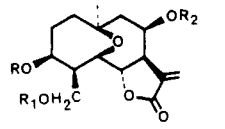
M. de los Angeles Gómez-Rodríguez, Martín Martínez-Ripoll, and Severino García-Blanco

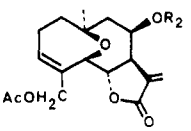
Instituto Rocasolano, CSIC, Departamento de Cristalografía, Serrano 119, 28006 Madrid, Spain

Received February 25, 1985

The plants of *Liatris* species have proved to be a rich source of chemically and biologically interesting sesquiterpene lactones.[1-3]

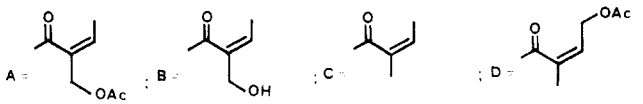
In previous articles,[4,5] Herz et al. reported the isolation of chapliatrin, isochapliatrin, and acetylchapliatrin. Recently,[6] an X-ray study of isochapliatrin has shown that the three previously known members of this series can be represented as **1a–c** and the five new compounds isolated from *Liatris gracilis* as **1d–g** and **2**.



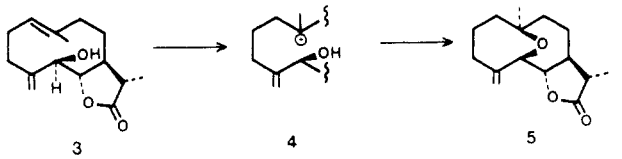


2 R_2 = B

1a R = H ; R_1 = Ac ; R_2 = A
1b R = Ac ; R_1 = H ; R_2 = A
1c R = R_1 = Ac R_2 = A
1d R = H ; R_1 = Ac ; R_2 = B
1e R = Ac ; R_1 = H ; R_2 = B
1f R = H ; R_1 = Ac ; R_2 = C
1g R = H ; R_1 = Ac ; R_2 = D

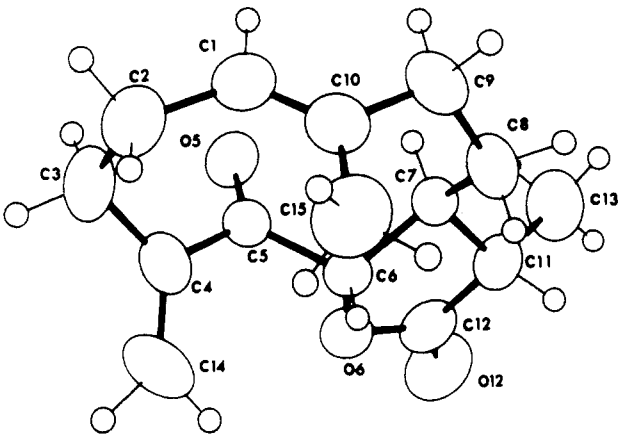


In order to evaluate the possible role played by compounds of type **3** in the biosynthesis of chapliatrin and its congeners, compound **3** was prepared; acid treatment of **3** should generate the cation **4**, which by cyclization should afford **5**, a compound of the type of chapliatrin.[7] Although

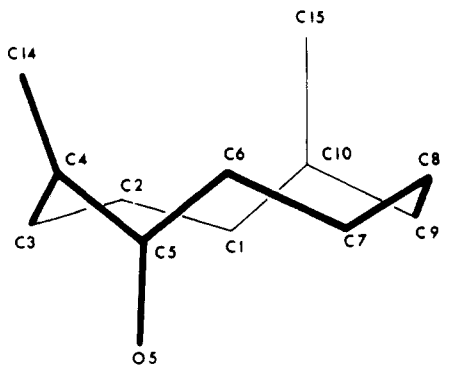


3 4 5

the planar representation used describes correctly the *R* and *S* configurations of C-5 and C-10, it does not give a good image of molecule **5**, since the oxygen bridge is on the α face.



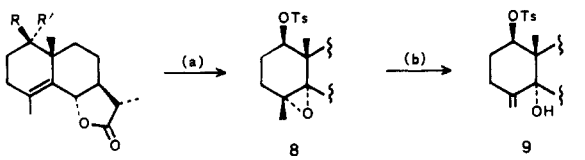
a



b

Figure 1. (a) Molecular structure of **10**. (b) Stereographic projection of the ten-membered ring of **10**.

Scheme I



6 R = R′ = O
7a R = OH ; R′ = H
7b R = OTs ; R′ = H

(a) MCPBA (b) BF_3-etherate

Compound **3** was prepared by using the ketone **6**[8] as starting material. Reduction and tosylation of **6** yielded the compound **7b**, which by epoxidation afforded the epoxide **8**; acid treatment (BF_3·Et_2O) of epoxide **8** yielded the hydroxy tosylate **9** (33% upon **6**) (Scheme I).

Compound **9** afforded stereoselectively[9] the germacradienone **10** (59%) upon treatment with KO-*t*-Bu–*t*-BuOH. The structure and absolute configuration of **10** were confirmed by X-ray diffraction. Figure 1a represents the final X-ray model of **10**, showing its absolute configuration as determined using the X-ray anomalous dispersion effects. The substituents C(14) and C(15) are β-oriented and O(5) is α-oriented. The double bond $\Delta^{1(10)}$ is trans and the ten-membered ring approximates to a *CCC* conformation,[11]

(1) Kupchan, S. M.; Davies, V. H.; Fujita, T.; Cox, M. R.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *38*, 1853.
(2) Herz, W.; Sharma, R. P. *J. Org. Chem.* **1975**, *40*, 199.
(3) Herz, W.; Sharma, R. P. *Phytochemistry* **1975**, *14*, 1561.
(4) Herz, W.; Wahlberg, I.; Stevens, CH. S.; Kalyanaraman, P. S. *Phytochemistry* **1975**, *14*, 1803.
(5) Herz, W.; Sharma, R. P. *J. Org. Chem.* **1976**, *41*, 1248.
(6) Herz, W.; Watanabe, K.; Blount, J. F. *Phytochemistry* **1984**, *23*, 373.
(7) The correct representation in the plane of the structures of chapliatrin and its congeners offers a certain number of difficulties. See the footnote on p 373 of ref 6.
(8) González, A. G.; Galindo, A.; Mansilla, H.; Gutiérrez, A. *Phytochemistry* **1981**, *20*, 2367.
(9) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
(10) (a) González, A. G.; Galindo, A.; Mansilla, H.; Gutiérrez, A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 881. (b) González, A. G.; Galindo, A.; Mansilla, H.; Palenzuela, J. A. *Tetrahedron Lett.* **1983**, *24*, 969.
(11) Hendrickson, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 7036.

0022-3263/85/1950-5856$01.50/0

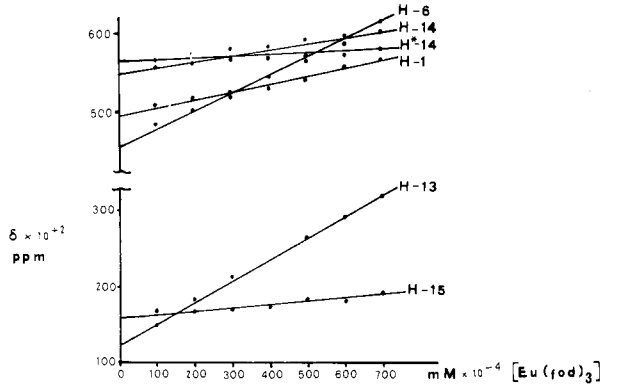
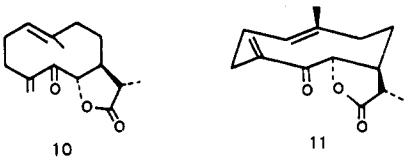


Figure 2. Lanthanoid-induced shifts for compound **10**.

although somewhat distorted due to the repulsion among the substituents. The lactone ring, attached to C(6) and C(7), shows an envelope conformation with C(7) at the flap, 0.446 (2) Å out of the plane defined by the other four atoms.

The conformational analysis in solution of **10** was made using ^{1}H NMR and LIS studies. The ^{1}H NMR spectra

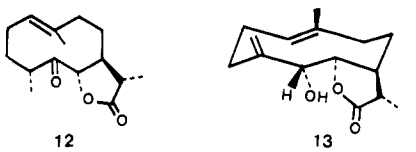


10 **11**

were taken at ordinary probe temperature (+35 °C) since none of the spectral features changed significantly at temperatures from −60 to +60 °C. The addition of Eu(fod)$_3$ caused the chemical shifts shown in Figure 2. Slight chemical shifts of the two protons on C-14 (H-14 and H*-14) in **10** are not compatible with a syn relationship of the carbonyl group at C-5 and the $\Delta^{4(14)}$ double bond, which suggests the *s*-trans disposition of the α,β-unsaturated ketone. Furthermore, the chemical shifts of H-1 suggest the syn-axial disposition of H-1 and the carbonyl group at C-5. These results strongly suggest that **11** is the favored conformation of **10** in solution, identical with that obtained by X-ray diffraction (Figure 1b).

The reduction of **10** with $NaBH_4$ afforded the target alcohol **3** (52%) and the ketone **12** (26%). The R configuration assigned at C-5 in **3** was based on the stereoselectivity of the reduction,[10] which takes place through the preferred conformation **11**. The re-face of the carbonyl group at C-5 is highly hindered and the attack by the hydride ion takes place on the si-face, yielding **3**.

Treatment of **3** with $CHCl_3$ saturated with HCl gas produced the oxide **5**. The formation of **5** is due to regioselective protonation of double bond $\Delta^{1(10)}$, via the preferred reacting conformation **13**. In **13** the 5-OH is



12 **13**

disposed axially and close to $\Delta^{1(10)}$, and the protonation is probably carried out with the assistance of 5-OH, yielding **5**.

The structure and absolute configuration of **5** were established by X-ray diffraction. Figure 3 is a perspective view of the molecular structure of **5**, showing its absolute configuration as determined by comparing the more relevant Bijvoet pairs. This absolute configuration agrees with that proposed for isochapliatrin[6] using the Cotton effect.

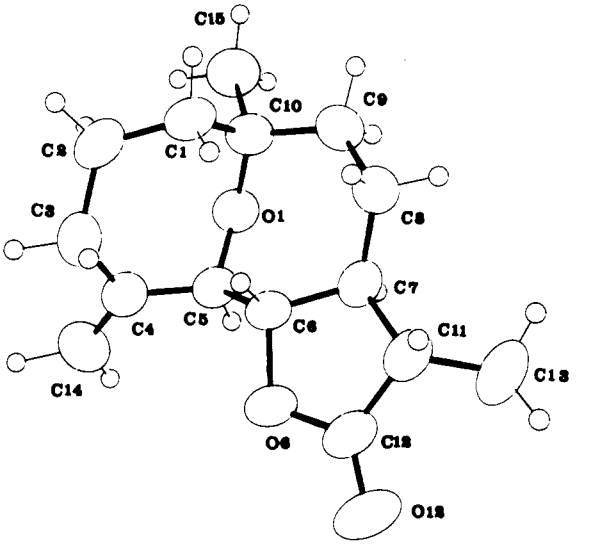


Figure 3. Molecular structure of **5**.

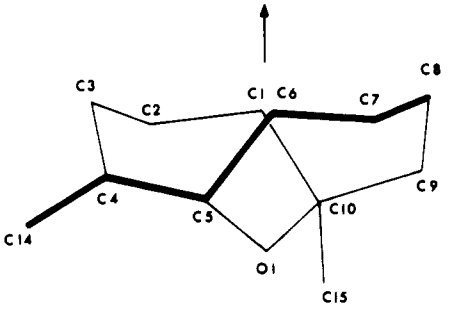


Figure 4. Stereographic projection of the two fused seven-membered rings of **5**.

The molecular conformation of isochapliatrin is also quite similar to that of the present compound **5**. Excluding the C(14) and C(15) substituents and the lactone ring, this molecule shows a pseudo-twofold axis symmetry, as indicated in Figure 4 and deduced from the torsion angles. Each seven-membered ring shows a twist-chair conformation,[11] although slightly distorted due to the influence between both rings and the substituents. The lactone ring, attached to C(6) and C(7), shows an envelope conformation, with C(7) at 0.531 (3) Å out of the plane defined by the other atoms of the ring.

The results suggest that type **3** compounds may be biogenetic precursors in the biosynthesis of chapliatrin and its congeners.

Experimental Section

Melting points were determined in a Kofler apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in the Instituto de Química Orgánica-C.S.I.C. with the help of a Perkin-Elmer 240 analyzer. IR spectra were determined on a Perkin-Elmer 257 spectrometer. ^{1}H NMR spectra were measured at 90 MHz in $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were obtained on a VG Micromass ZAB-2F. Unless otherwise stated, column chromatography was carried out with Merck silica gel (0.065–0.2 mm).

Reduction of Ketone 6. Sodium borohydride (175 mg) dissolved in EtOH (5 mL) was added to 3.85 g of **6** dissolved in EtOH (50 mL) and stirred for 150 min at room temperature. The solution was then concentrated under reduced pressure, poured over water, extracted with EtOAc, dried, and chromatographed. Elution with benzene–EtOAc yielded **7a** (83%): mp 172–174 °C (petroleum ether–EtOAc 7:3); $[\alpha]_D$ +60.7° (*c* 0.4); IR bands at 3600, 1770, and 1605 cm^{-1}; NMR signals 4.59 d (J = 8 Hz, H-6), 3.51 dd (J = 9 and 10 Hz, H-1), 1.84 s (H-14), 1.21 d (J = 7 Hz,

H-13), 1.10 s (H-15); MS 250 (M^+), 232 ($M^+ - 18$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.29; H, 8.80.

Tosylation of 7a. Tosyl chloride (3 g) was added to 3.22 g of **7a** dissolved in dry pyridine and the mixture was kept at room temperature for 20 h, then poured over ice water, extracted with EtOAc, washed, dried, and chromatographed. Elution with petroleum ether–EtOAc (1:1) produced **7b** (90%): mp 119–120 °C dec (petroleum ether–EtOAc); $[\alpha]_D$ +40° (*c* 0.3); IR bands at 1770 and 1600 cm^{-1}; NMR 7.82 d (J = 8 Hz, Ts), 7.36 d (J = 8 Hz, Ts), 4.50 m (H-6 and H-1), 2.45 s (Ts), 1.81 s (H-14), 1.17 d (J = 7 Hz, H-13), 1.11 s (H-15); MS 232 ($M^+ - 172$).

Epoxidation of 7b. *m*-Chloroperbenzoic acid (4.5 g) was added to 2.7 g of **7b** dissolved in CH_2Cl_2 (20 mL) and stirred for 14 h at room temperature. Excess MCPBA was destroyed by Na_2SO_3 solution, and the mixture was neutralized with $NaCO_3H$, extracted with $CHCl_3$, washed, dried, concentrated, and chromatographed. Elution with petroleum ether–EtOAc (7:3) yielded **8** (89.7%) oil, $[\alpha]_D$ +34.1° (*c* 0.6); IR bands at 1775 and 1660 cm^{-1}; NMR 7.80 d (J = 9 Hz, Ts), 7.36 d (J = 9 Hz, Ts), 4.67 dd (J = 7 and 6 Hz, H-1), 4.28 d (J = 11 Hz, H-6), 2.46 s (Ts), 1.49 s (H-14), 1.24 d (J = 7 Hz, H-13), 1.12 s (H-15); MS 420 (M^+), 248 ($M^+ - 172$).

Preparation of 9. Boron trifluoride etherate, freshly distilled (0.1 mL), was added to a solution of epoxide **8** (100 mg) in toluene (5 mL), and the mixture was stirred at −30 °C for 19 h under nitrogen. The mixture was poured into water, washed with saturated $NaHCO_3$, extracted with $CHCl_3$, dried, concentrated, and chromatographed. Elution with petroleum ether–EtOAc (7:3) yielded 50 mg (50%) of **9**: mp 197–199 °C dec (CH_2Cl_2–petroleum ether); $[\alpha]_D$ +106.3° (*c* 0.47); IR bands at 3430, 1780, 1650, and 1600 cm^{-1}; NMR 7.82 d (J = 8 Hz, Ts), 7.35 d (J = 8 Hz, Ts), 4.85 and 5.22 m (H-1 and H-14), 4.18 d (J = 10 Hz, H-6), 2.43 s (Ts), 1.20 d (J = 6 Hz, H-13), 0.90 s (H-15); MS 420 (M^+), 248 ($M^+ - 172$). Anal. Calcd for $C_{22}H_{28}O_6S$: C, 62.85; H, 6.66; S, 7.61. Found: C, 63.08; H, 7.09; S, 7.43.

Basic Treatment of 9. Potassium *tert*-butoxide (900 mg), dissolved in *t*-BuOH (20 mL), was added to a solution of **9** (3.26 g) in *t*-BuOH (200 mL), and the mixture was stirred at 42 °C for 28 h under nitrogen. Excess of the *t*-BuOH was eliminated by evaporation, and the mixture was acidified with HCl solution (10%), extracted with $CHCl_3$, washed, dried, concentrated, and chromatographed. Elution with petroleum ether–EtOAc yielded **10** (58%): mp 87–89 °C (CH_2Cl_2–petroleum ether); $[\alpha]_D$ +245° (*c* 0.4); IR bands at 1780 and 1695 cm^{-1}; NMR 5.71 d (J = 3 Hz, H-14), 5.05 m (H-1), 4.71 d (J = 8 Hz, H-6), 1.56 s (H-15), 1.33 d (J = 6 Hz, H-13); MS 248.1418 ($C_{15}H_{20}O_3$; high resolution), 233.1194 ($C_{14}H_{17}O_3$).

Similar treatment with aqueous 1 N KOH (room temperature, 30 min) yielded identical results (59%).

X-ray Structure Determination of 10. $C_{15}H_{20}O_3$, crystallizes in the monoclinic space group $P2_1$ with Z = 2, a = 10.446 (1) Å, b = 7.8994 (3) Å, c = 8.8555 (4) Å, β = 105.854 (3)°, and V = 702.9 (1) Å^3. The molecular weight is 248.32 and the calculated density is 1.17 g cm^{-3}. The intensities of the 1294 independent Friedel pairs up to θ = 65° were alternately collected using a $w/2\theta$ scan technique on a PW1100 diffractometer equipped with graphite monochromated Cu Kα radiation (λ = 1.541 78 Å). The crystal size was 0.3 × 0.2 × 0.4 mm. No crystal decomposition was detected. After Lorentz and polarization corrections, 1069 Friedel pairs were considered as observed with $I > 2\sigma(I)$. No absorption correction was applied (μ = 6.13 cm^{-1}). Scattering factors for neutral atoms and the anomalous dispersion corrections for C and O were taken from the literature.[12]

The structure was solved by MULTAN[13] and refined by fullmatrix least-squares analysis. A convenient weighting scheme[14] was used to prevent bias on $\langle w\Delta^2F\rangle$ vs. $\langle F_o\rangle$ and vs. $\langle \sin\theta/\lambda\rangle$. Several cycles of weighted anisotropic refinement (H atoms as fixed isotropic contributors), including both hkl and $\bar{h}\bar{k}\bar{l}$ reflections, gave the discrepancy indices R = 0.037 and R_w = 0.046.[15] The absolute configuration of **10** was determined by comparing the 27 more relevant Bijvoet pairs[16] ($\Delta F_c > 0.06$), giving an average Bijvoet difference of 0.178 (vs. 0.219 for the reverse enantiomer) and an average Bijvoet ratio of 1.014 (vs. 1.021).

Reduction of 10. Sodium borohydride (15 mg) dissolved in MeOH (2 mL) was added to 194 mg of **10** dissolved in MeOH (10 mL, 0 °C), and the mixture was stirred for 44 h at room temperature. The excess MeOH was removed by evaporation, and the mixture was acidified with HOAc solution (1%), extracted with EtOAc, washed, dried, concentrated, and chromatographed on silica gel impregnated with 15% $AgNO_3$. Elution with petroleum ether–EtOAc (9:1) yielded **3** (52%) and **12** (26%).

Compound 3, oil, $[\alpha]_D$ −3.39° (*c* 0.2); IR bands at 3610 and 1765 cm^{-1}; NMR (CCl_4) 5.55 s (H-14), 5.36 m (H-1), 5.07 s (H*-14), 4.05–4.40 complex (H-5 and H-6), 1.64 s (H-15), 1.33 d (J = 8 Hz, H-13); MS 250.1573 ($C_{15}H_{22}O_3$; high resolution), 233.1522 ($C_{15}H_{21}O_2$), 204.1468 ($C_{14}H_{20}O$).

Compound 12, mp 108–110 °C, (CH_2Cl_2–petroleum ether); $[\alpha]_D$ −60.2° (*c* 0.2); IR bands at 1775 and 1715 cm^{-1}; NMR 4.78 m (H-1), 4.32 d (J = 7 Hz, H-6), 1.68 s (H-15), 1.25 d (J = 7 Hz, H-13), 1.08 d (J = 7 Hz, H-14); MS 250.1570 ($C_{15}H_{22}O_3$; high resolution).

Acid Treatment of 3. Compound **3** (246 mg) was dissolved in $CHCl_3$ (6 mL), through which HCl gas had been bubbled for 1 min. The mixture was stirred at room temperature for 25 h, diluted with $CHCl_3$, washed with $NaHCO_3$ solution (1%) and then water, dried, concentrated, and chromatographed on silica gel impregnated with $AgNO_3$ (15%). Elution with petroleum ether–EtOAc (9:1) yielded **5** (44%): mp 80–82 °C; $[\alpha]_D$ −3.57° (*c* 0.14); IR bands at 1780 and 1640 cm^{-1}; NMR 5.01 s (H-14), 4.95 s (H*-14), 4.78–4.15 complex (H-5 and H-6), 1.25 s (H-15), 1.25 d (J = 7 Hz, H-13); NMR (C_6D_6) 5.06 s (H-14), 4.87 s (H*-14), 4.31 d (J = 8 Hz, H-5), 3.85 dd (J = 9 and 10 Hz, H-6), 1.08 s (H-15), 0.99 d (J = 7 Hz, H-13); MS 250.1575 ($C_{15}H_{22}O_3$; high resolution), 232.1473 ($C_{15}H_{20}O_2$).

X-ray Structure Determination of 5. $C_{15}H_{22}O_3$, space group $P2_1$, Z = 2, a = 12.241 (2) Å, b = 7.5293 (3) Å, c = 7.619 (1) Å, β = 92.808 (5)°, V = 701.3 (2) Å^3, mol wt 250.34, and calculated density 1.18 g cm^{-3}. The intensities of 1131 independent Friedel pairs up to θ = 60° were alternately collected with a $w/2\theta$ scan, using a PW1100 diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å); crystal size 0.4 × 0.3 × 0.2 mm. No intensity decay was detected. No absorption correction was applied (μ = 6.15 cm^{-1}). After Lorentz and polarization corrections, 924 Friedel pairs were considered as observed with the criterion $I > 2\sigma(I)$. Scattering factors used[12] and anomalous dispersion corrections for C and O were those for neutral atoms. The structure was solved by MULTAN[13] and refined by fullmatrix least-squares, using a weighting scheme[14] to prevent bias on $\langle w\Delta^2F\rangle$ vs. $\langle F_o\rangle$ and vs. $\langle \sin\theta/\lambda\rangle$. Hydrogen atoms were considered as fixed isotropic contributors and both hkl and $\bar{h}\bar{k}\bar{l}$ reflections were used. Last discrepancy indices were R = 0.037 and R_w = 0.045.[15] The absolute configuration of **5** was confirmed by comparing the 37 more relevant Bijvoet pairs[16] ($\Delta F_c > 0.05$), giving an average Bijvoet difference of 0.099 (vs. 0.187 for the reverse enantiomer) and an average Bijvoet ratio of 1.012 (vs. 1.023).

Acknowledgment. This work was subsidized in part by the Comisión Asesora de Investigación Científica y Técnica (Grant No. 3190/1984), Spain. M.A.G.R., A.G., and J.A.P. thank the C.S.I.C. for a research grant.

Registry No. **3**, 99267-90-0; **5**, 99280-63-4; **6**, 23522-05-6; **7a**, 41410-55-3; **7b**, 99297-03-7; **8**, 99267-87-5; **9**, 99267-88-6; **10**, 99267-89-7; **12**, 99297-04-8.

Supplementary Material Available: A listing of positional and thermal parameters and bond distances and angles for **5** and **10** (8 pages). Ordering information is given on any current masthead page.

(12) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, 1974; Vol. IV.
(13) Main, P. "MULTAN 80"; Physics Department, University of York: York, England, 1980.
(14) Martínez-Ripoll, M.; Cano, F. H. "PESOS", Departamento de Cristalografía, Instituto Rocasolano, Serrano 119, 28006 Madrid, Spain, 1975.
(15) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. "The X-ray 76 System"; Computer Science Center, University of Maryland: College Park, MD, 1976.
(16) Martínez-Ripoll, M.; Fayos, J. *Z. Kristallogr.* **1980**, *152*, 189.