Synthesis of Enantiopure 2,3,8,8a-Tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine Derivatives†

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Introduction

The synthesis of antianginous and antihypertensive agents has attracted the interest of organic chemists for a long time.[1] In this area, 1,4-dihydropyridines (**1**) emerged as very potent calcium antagonists, easy to synthesize by the Hantzsch methodology in a one-pot process from keto esters, aldehydes, and ammonia.[2] Many derivatives have been obtained by different research groups from universities and industries, mainly directed to the modification of the substituents on the basic skeleton of the dihydropyridine[3] with the aim of finding more selective and longer-acting therapeutic agents. Racemic and enantiopure compounds have been tested in the search for new compounds with improved activity and a better pharmacological profile.[4] In this field, we have been working on several kinds of derivatives[5] and have finally obtained the very promising long-lasting antihypertensive tetrahydrooxazolopyridine **2** derivatives.[6] This class of compounds is structurally related to the active dihydropyridines, but with two main differences: (1) a substitution on the N-atom, which usually decreases the antihypertensive activity,[7] and (2) an additional oxazolidine ring fused to the *a*-bond of the hydropyridine structure.

In this research, we studied the regioselectivity of the reaction between unsaturated keto esters and enamines of ethanolamine,[8] which produced the tetrahydrooxazolopyridine system in approximately 50% yield in a one-step process. The presence or absence of ester substituents on the unsaturated carbonyl substrate changes the regiochemistry of the reaction, directing the cyclization of the oxazolidine moiety to positions 2 or 6 of the pyridine ring, respectively. Further transformations of this system have also been accomplished[9] in order to prepare new derivatives, by modification of the substituents in the tetrahydropyridine ring or functionalization of the oxazolidine ring. These modifications are of interest in the study of structure−activity relationships and the mechanism of action of this class of compounds, which are not calcium antagonists like the parent dihydropyridines.

The synthesis of pure enantiomers is necessary to ascertain the activity of each enantiomer. Different approaches have been described for asymmetric induction in the Hantzsch reaction,[10] mainly based on the use of chiral esters, sulfoxides, and other substituents in the starting enamine or in the Michael acceptor.[11] In other cases, the resolution of racemic mixtures through their diastereomeric salts or esters[12] or by enzymatic resolution[13] has been used to prepare pure enantiomers from racemic dihydropyridines obtained in the Hantzsch reaction. Asymmetric synthesis of dihydropyridines by other methodologies has also been described.[14] To achieve the enantioselective synthesis of the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine system (**2**), the use of chiral enamines formed from chiral amino alcohols is another possibility that could produce high diastereoselectivity, thus leading to enantiopure representatives of this class of antihypertensive agents. A related methodology has been used for the synthesis of dihydropyridines by the Hantzsch reaction.[15]

In this paper, we describe a procedure for the enantioselective synthesis of compounds **3** using enamines from (*R*)- and (*S*)-1-amino-2-propanol. In this process, it is noticeable that the formation of three new stereocenters in the tetrahydropyridine ring is controlled by the presence of a single chiral carbon atom in the starting enamine, placed three, four, and five bonds away from these newly created stereocenters.

Results and Discussion

Following the previously described methodology,[6,8] we began the preparation of 2- and 3-substituted 2,3,8,8a-

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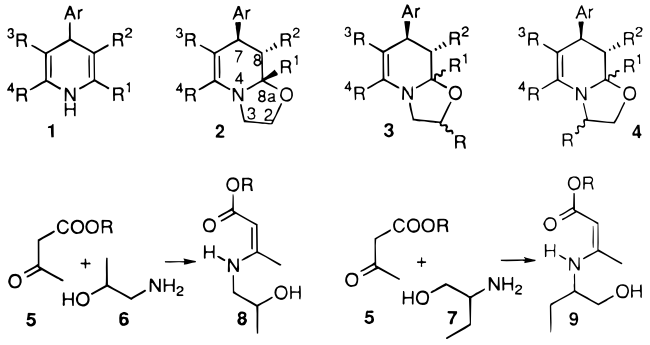
tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines (**3** and **4**) using conveniently substituted enamines from amino alcohols. Starting from *β*-keto esters **5** and racemic 1-amino-2-propanol (**6**), the racemic enamine **8** was obtained, and from racemic 2-amino-1-butanol (**7**) enamine **9** was produced.



When these enamines were employed in the synthesis of the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines, 2- or 3-substituted derivatives were isolated in yields comparable to those previously described, but from enamines **8** only one stereoisomer of **3** was produced, while from enamines **9** two diastereomeric products **4** were obtained. The relative stereochemistry of type **3** compounds at C-8a and C-7 can be easily established as *cis*-1,3-diaxial by the shielding of the methyl group at C8a (0.90 ppm) and that at C-8 as *trans*-1,2-diaxial by the coupling constant between H-7 and H-8 (∼0 Hz), which are the same relative stereochemistries at C-7, C-8, and C-8a as those produced for the unsubstituted **2**.[8] Thus, the reaction is stereospecific, and only the relative stereochemistry at C-2 was not established at that time.

From the starting material **9**, it is possible that the resulting diastereomers **4** could have different relative stereochemistries at C-3 or at C-8a. Molecular modeling studies suggest that the most stable conformations for C-3 epimers, with the same C-8a configuration, maintain the same disposition of C-7 and C-8a substituents: *cis* 1,3-diaxial (Me at C-8 shielded) or *trans* 1,3-dipseudo-equatorial (Me at C-8a deshielded). As a consequence of the observed shielding of Me−C8a, both stereoisomers of **4** most likely differ in the relative stereochemistry at C-8a.

The above results clearly demonstrated that the stereochemistry of the chiral center of the enamine produces a total chiral induction in the three new centers C-7, C-8, and C-8a created in the synthesis of 2-substituted 2,3,8,-8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines **3**. In conclusion, it may be possible to accomplish the enantioselective synthesis of the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]-pyridine system using the diastereospecific reaction of enantiopure enamines of type **8**.

Accordingly, both enantiomers (2′*R*)-**8ar** and (2′*S*)-**8as** of methyl 3-((2-hydroxypropyl)amino)but-2(*Z*)-enoate were prepared from pure commercial enantiomers of 1-amino-2-propanol and methyl acetylacetate. From ethyl, benzyl, and *tert*-butyl acetylacetates enantiopure **8br**, **8cs**, and **8dr** were obtained. These enamines were used in the cyclization reaction, producing the usual yields of the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines **3** (Scheme 1). The enantiomeric purity of these derivatives was checked using chiral lanthanide shift reagents in ^{1}H-NMR, which produced a duplicity of representative signals in the spectra of racemic **3a** but no duplicity in

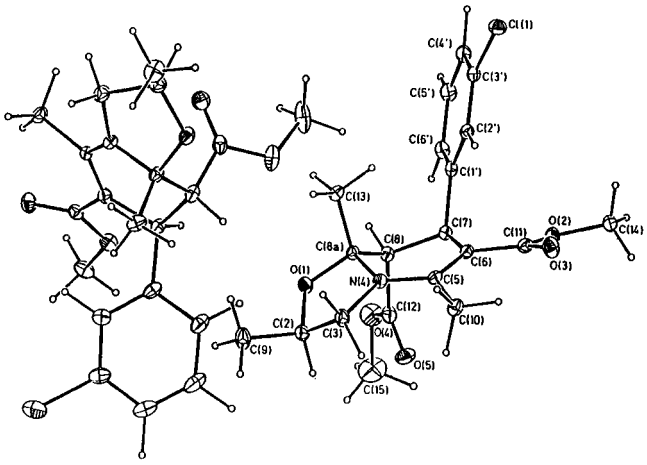
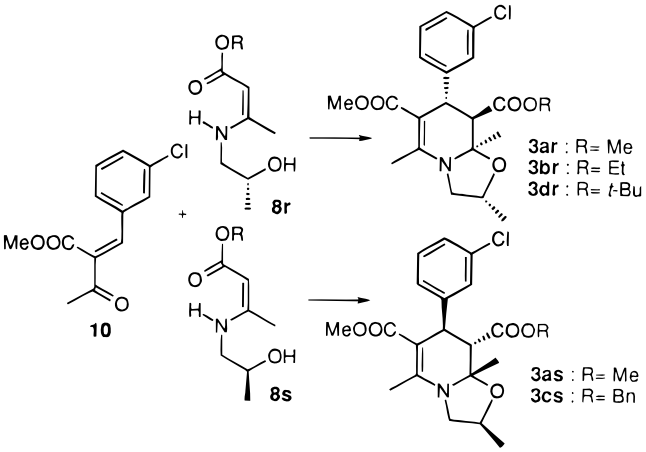


Figure 1. ORTEP drawing of compound **3ar**, showing two conformers present in the unit cell.

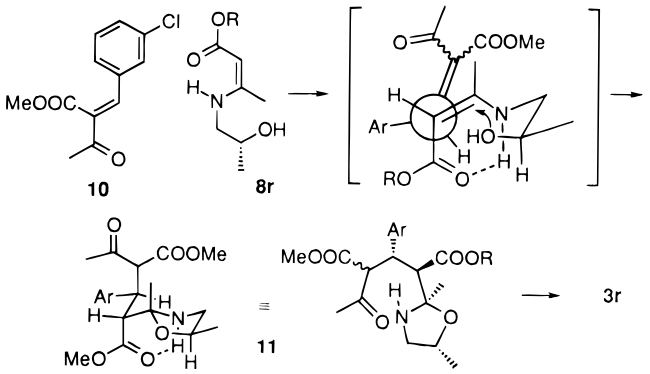
Scheme 1. Synthesis of Enantiopure 2,3,8,8a-Tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines 3 from Enamines 8



any of the pure **3ar**, **3as**, **3br**, **3cs**, and **3dr** products (detection limit <3%). When pure **3ar** containing shift reagent and **3as** containing an equal amount of the same shift reagent were mixed, the spectrum of the resulting mixture was identical to the spectrum of the racemic mixture containing the same duplicate signals.

Once the enantioselective synthesis of **3** by this methodology was proved, only the stereochemistry of the C7−C8a moiety relative to that of C2 remained to be established. The absence of an NOE on Me−C2 or H-2 upon irradiation of the Me−C8a was interpreted as a *cis*-relationship between Me−C8a and Me−C2. To confirm the proposed stereochemistry of type **3** compounds, substance **3ar** was subjected to X-ray diffraction, and an ORTEP drawing of the structure is shown in Figure 1. As shown, there are two conformers in the unit cell, but the differences between them are very small and they show the same spatial arrangements. These differences mainly appear in the conformation of the oxazolidine ring, since the torsion angles are less than 10° in all cases except for those affecting the oxazolidine ring and the carboxylate on C8: C8a−O1−C2−C3, C7−C8−C12−O4, C8a−C8−C12−O5, C8a−O1−C2−C9, C2−O1−C8a−C8, C7−C8−C12−O5, and C8a−C8−C12−O4, which are in the 10°−20° range. In both conformations, the spatial arrangement of the aromatic ring and the Me−C8a are those suggested by ^{1}H-NMR data, and theoretical calculations obtained by molecular mechanics (Macromodel

Scheme 2. Mechanistic Proposal for the Stereocontrolled Cyclization



4.0) and are in agreement with the absence of NOE's between Me−C8a and H2 or Me−C2. Consequently, the proposed *cis* relative stereochemistry between Me−C8a and Me−C2 was unequivocally established in this derivative, which has the structure (2*R*,7*S*,8*R*,8a*R*)-dimethyl 7-(3-chlorophenyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate (**3ar**). The lack of an appreciable coupling between H-7 and H-8 is also in agreement with their dihedral angles (-88.7° and −83.5°) measured for the conformers.

In a previous paper,[8] we included a mechanistic proposal to account for the formation of different regioisomers of the tetrahydrooxazolopyridines and other reaction products having the cyclohexane skeleton. The mechanism should also explain the stereospecificity of the reaction. Our proposal was based on the necessary formation of the oxazolidine ring prior to the tetrahydropyridine ring in the pathway to tetrahydrooxazolopyridines because separate experiments demonstrated that *N*-hydroxyethyldihydropyridines do not cyclize under the reaction conditions. All the reaction products with cyclohexane and tetrahydrooxazolopyridine skeletons contain a new C−C bond, linking the β-position of the enamine and the β-position of the unsaturated keto ester, and its formation is proposed as the first step for this reaction.[16] In this step, the C-7 and C-8 stereocenters are generated. The stereochemistry at C-8a is generated during the formation of the oxazolidine ring and must be directly governed by the stereochemistry of the hydroxyalkyl chain attached to the N atom of the enamine.

During the Michael addition, electron density diminishes in the enamine and may be compensated by the electron pairs of the close hydroxylic oxygen. Both steps could be simultaneous, thus producing the Michael addition−oxazolidine cyclization intermediate **11** depicted in Scheme 2. In this process, all the stereocenters are generated from the chiral center of the enamine, and hence, the most favored approach of the reagents must produce the resulting stereochemistries. As depicted, the methyl group of the hydroxypropylamine, which governs the stereochemistry, is maintained distant from the rest of the molecule in a favorable disposition for the attack by the hydroxyl group to the electron deficient α-position of the enamine. Moreover, it is proposed that the favorable approach between the enamine and the unsaturated ester would take place with both double bonds, having opposite polarizations, in a *syn* relationship and the remaining substituents avoiding the appearance of strong interactions. The C−H bonds close to C−Ar and C−COOMe bonds during the approach allow a reaction process with low hindrance and good charge stabilization, thus yielding intermediate **11**. The closure of **11** toward the tetrahydropyridine ring produces the final product **3**.

Experimental Section

For general experimental details see refs 6 and 8. Optical rotations were measured at 25 °C on a digital Perkin-Elmer 241 polarimeter in a 1 dm cell.

General Procedure. A mixture of the unsaturated keto ester **10** (20 mmol) and enamines **8** or **9** (20 mmol) in MeOH (50 mL) was refluxed for 24 h. The solvent was removed, and the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines were isolated in 37−48% yield after flash chromatography (Hex/AcOEt) and/or crystallization.

(+)-(2*R*,7*S*,8*R*,8a*R*)-Dimethyl 7-(3-chlorophenyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate (3ar): 48% yield; mp 130−131 °C (MeOH); $[\alpha]_D = +74.4°$ (*c* 0.82, $CHCl_3$); IR (KBr) 1750, 1690, 1590; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.27 (3H, d, $J = 5.8$ Hz), 2.59 (3H, d, $J = 1.3$ Hz), 3.25 (1H, m), 3.27 (1H, m), 3.44 (3H, s), 3.71 (3H, s), 4.08 (1H, m), 4.12 (1H, m), 4.27 (1H, s), 7.0−7.4 (4H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 18.7 (q), 20.5 (q), 28.7 (q), 41.0 (d), 50.5 (q), 51.7 (q), 52.7 (t), 53.2 (d), 72.8 (d), 90.4 (s), 92.5 (s), 125.9 (d), 126.3 (d), 127.9 (d), 129.5 (d), 134.3 (s), 147.5 (s), 152.0 (s), 169.3 (s), 171.6 (s). Anal. Calcd for $C_{20}H_{24}ClNO_5$: C, 60.99; H, 6.14; N, 3.56. Found: C, 60.61; H, 6.33; N, 3.65.

(−)-(2*S*,7*R*,8*S*,8a*S*)-Dimethyl 7-(3-chlorophenyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate (3as): 40% yield; mp = 128−129 °C (MeOH); $[\alpha]_D = -70.8°$ (*c* 0.82, $CHCl_3$). Anal. Calcd for $C_{20}H_{24}ClNO_5$: C, 60.99; H, 6.14; N, 3.56. Found: C, 60.75; H, 6.18; N, 3.70.

(+)-(2*R*,7*S*,8*R*,8a*R*)-Methyl 7-(3-chlorophenyl)-8-(ethoxycarbonyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo-[3,2-*a*]pyridine-6-carboxylate (3br): 40% yield; $[\alpha]_D = +26.3°$ (*c* 0.38, $CHCl_3$); IR (film) 1730, 1680, 1600, 1580; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.27 (3H, d, $J = 5.7$ Hz), 1.31 (3H, t, $J = 7.1$ Hz), 2.60 (3H, s), 3.25 (1H, m), 3.27 (1H, m), 3.44 (3H, s), 4.03 (1H, m), 4.12 (1H, m), 4.18 (2H, c, $J = 7.1$ Hz), 4.28 (1H, s), 7.11−7.29 (4H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 14.2 (q), 18.6 (q), 20.3 (q), 28.6 (q), 40.9 (d), 50.5 (q), 52.5 (t), 53.2 (d), 60.4 (t), 72.7 (d), 90.3 (s), 92.5 (s), 125.9 (d), 126.3 (d), 127.7 (d), 129.4 (d), 134.2 (s), 147.5 (s), 151.1 (s), 169.3 (s), 171.2 (s). Anal. Calcd for $C_{21}H_{26}ClNO_5$: C, 61.84; H, 6.42; N, 3.43. Found: C, 61.46; H, 6.51; N, 3.75.

(+)-(2*S*,7*R*,8*S*,8a*S*)-Methyl 7-(3-chlorophenyl)-8-(benzyloxycarbonyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (3cs): 45% yield; mp = 126−127 °C (Et_2O); $[\alpha]_D = +33.5°$ (*c* 0.65, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, s), 1.16 (3H, d, $J = 5.8$ Hz), 2.54 (3H, s), 3.27 (1H, m), 3.32 (1H, m), 3.44 (3H, s), 3.69 (1H, m), 3.97 (1H, m), 4.30 (1H, s), 5.07 (1H, d, $J = 12.4$ Hz), 5.22 (1H, d, $J = 12.4$ Hz), 7.12−7.25 (9H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 18.7 (q), 20.3 (q), 28.7 (q), 40.9 (d), 50.5 (q), 52.5 (t), 53.5 (d), 66.3 (t), 72.6 (d), 90.4 (s), 92.5 (s), 125.9 (d), 126.3 (d), 127.9 (d), 128.2 × 2 (d), 128.5 × 3 (d), 129.5 (d), 134.3 (s), 136.1 (d), 147.4 (s), 152.0 (s), 169.3 (s), 171.1 (s). Anal. Calcd for $C_{26}H_{28}ClNO_5$: C, 66.45; H, 6.01; N, 2.98. Found: C, 66.73; H, 6.23; N, 3.03.

(+)-(2*R*,7*S*,8*R*,8a*R*)-Methyl 7-(3-chlorophenyl)-8-(*tert*-butyloxycarbonyl)-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (3dr): 37% yield; mp = 118−119 °C (MeOH); $[\alpha]_D = +71.1°$ (*c* 0.98, $CHCl_3$); IR (KBr) 1740, 1690, 1570; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, s), 1.27 (3H, d, $J = 6.0$ Hz), 1.47 (9H, s), 2.59 (3H, s), 3.13 (1H, m), 3.25 (1H, m), 3.44 (3H, s), 4.05 (1H, m), 4.16 (1H, m), 4.22 (1H, s), 7.09−7.27 (4H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 18.7 (q), 20.4 (q), 28.2 × 3 (q), 28.7 (q), 41.0 (d), 50.4 (q), 52.6 (t), 54.4

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(d), 72.7 (d), 80.5 (s), 90.5 (s), 92.3 (s), 125.9 (d), 126.2 (d), 127.9 (d), 129.4 (d), 134.2 (s), 147.9 (s), 151.2 (s), 169.4 (s), 171.3 (s). Anal. Calcd for $C_{23}H_{30}ClNO_5$: C, 63.37; H, 6.94; N, 3.21. Found: C, 63.09; H, 6.98; N, 2.96.

(±)-Dimethyl 7-(3-Chlorophenyl)-3-ethyl-5,8a-dimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate (4). Following the same methodology previously described, an unresolved 6:4 mixture of two diastereomers of **4** was obtained from enamine **9** (43%). The spectroscopic data were observed for each component in the mixture. Major: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.2 Hz), 1.32 (3H, s), 1.69 (2H, m), 2.47 (3H, d, J = 1.1 Hz), 2.52 (1H, d, J = 12.0 Hz), 3.30 (3H, s), 3.45 (3H, s), 3.83 (1H, m), 3.99 (1H, d, J = 9.0 Hz), 4.03 (1H, dd, J_1 = 1.1 Hz, J_2 = 12.0 Hz), 4.12 (1H, dd, J_1 = 5.0 Hz, J_2 = 9.0 Hz), 7.0−7.4 (4H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 10.7 (q), 17.6 (q), 18.6 (q), 26.6 (t), 44.3 (d), 50.0 (q), 51.7 (q), 59.2 (d), 59.7 (d), 68.0 (t), 92.0 (s), 101.6 (s), 125.5 (d), 126.4 (d), 127.0 (d), 129.4 (d), 134.1 (s), 147.0 (s), 150.0 (s), 167.6 (s), 171.6 (s). Minor: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 0.90 (3H, s), 1.69 (2H, m), 2.57 (3H, d, J = 1.1 Hz), 3.33 (1H, s), 3.43 (3H, s), 3.72 (3H, s), 3.83 (1H, m), 3.81 (1H, d, J = 9.0 Hz), 4.12 (1H, dd, J_1 = 5.0 Hz, J_2 = 9.0 Hz), 4.33 (1H, br s), 7.0−7.4 (4H, m); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 11.2 (q), 18.7 (q), 24.7 (q), 28.1 (t), 41.3 (d), 50.4 (q), 51.7 (q), 53.7 (d), 59.7 (d), 67.5 (t), 90.7 (s), 92.0 (s), 125.8 (d), 126.2 (d), 127.3 (d), 129.4 (d), 134.1 (s), 147.0 (s), 152.0 (s), 167.6 (s), 171.6 (s).

Single-Crystal X-ray Structure Determination of 3ar. Colorless crystal, size 0.46 × 0.33 × 0.20 mm. $C_{20}H_{24}Cl_1N_1O_5$, M_r = 393.87, monoclinic, space group $P2_1$, a = 10.497(4) Å, b = 10.504(4) Å, c = 18.536(5) Å, β = 100.81(2) V = 2008(1) Å^3, Z = 4, D_x = 1.30 M g m^{-3}, Mo Kα radiation (graphite crystal monochromator, λ = 0.710 73 Å), μ = 0.220 cm^{-1}, $F(000)$ = 832, T = 293 K. Final conventional R = 0.049 (for 4804 $F_o > 4\sigma(F_o)$) and wR^2 = 0.136 (for all reflections), $w = 1.0/[\sigma^2(F_o^2) + (0.0893P)^2]$ where $P = (\max(F_o^2, 0) + 2*F_c^2)/3$. Total number of parameters 488. The intensity data of 7718 reflections in hkl range (−12, −12, −22) to (12, 12, 22) and θ limits ($0 < \theta < 25°$) were measured, using the $\omega - 2\theta$ scan technique. Profile analysis was performed on all reflections.[17] The structure was solved by Patterson interpretation using the program SHELXS86. Isotropic least-squares refinement, using a local version of SHELX76,[18] converged to R = 0.101. At this stage an empirical absorption correction was applied using DIFABS,[19] and further refinements were carried out on $/F/^2$ using the program SHELXL93.[20] Absolute configuration was checked (Flack parameter[21] χ = 0.02(7)). Atomic scattering factors were taken from *International Tables for X-ray Crystallography*.[22] Geometrical calculations were made with PARST.[23] The crystallographic plots were made with EUCLID.[24] All calculations were made at the University of Oviedo on the Scientific Computer Center and X-ray group VAX-computers.

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Supporting Information Available: Copies of ^{1}H-NMR spectra of **3ar**, **3as**, racemic **3a**, and Eu(tfc)$_3$ displacement experiments and a table of ^{13}C NMR assignments (9 pages). This material is contained in 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.

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