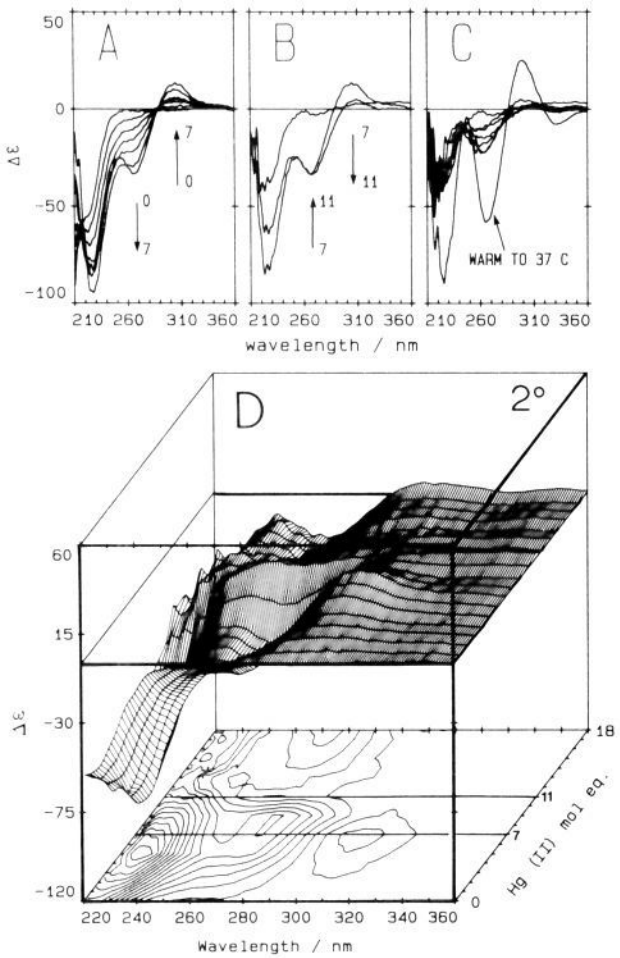

Figure 2. CD spectra recorded at 2 °C during a titration of rabbit liver apo-MT 2 with Hg(II) at pH 2.4. (A) 0–7 (0, 1, 2, 3, 4, 5, 7); (B) 7–11 (7, 9, 11); (C) 11–18 (11, 12, 13, 14, 15, 17, 18) mol equiv of Hg at 2 °C, and the spectrum for 18 mol equiv measured at 37 °C; (D) 0–18 mol equiv, the third axis in (D) is mol equiv of Hg.

reaction is not reversible, and the Hg_{18}-MT CD spectrum remains if the temperature is subsequently reduced to 2 °C. There is no free Hg at either temperature.

The spectrum observed for Hg_{18}-MT 2 in this wavelength region arises from $RS^- \rightarrow Hg^{2+}$ transitions. The high CD intensity observed for Hg_{18}-MT must arise from a strongly chiral environment for the Hg–S bonds. It is not possible for such an intensely dichroic signal to be generated if the structure of Hg_{18}-MT was a random coil. Because the CD spectrum is specifically sensitive (due to exciton coupling effects[10]) to formation of clustered species, like Cd_4-SR_{11},[4,10,17,18] a 3-dimensional structure is necessary in order to generate the CD spectrum observed when 18 Hg atoms are bound to the 20 thiolate groups in MT 2 below pH 7. This is highly unexpected. There is no evidence of dimer formation,[19] and it is unlikely that Hg_{18}-MT adopts the Cd_7S_{20}, 2-domain structure, because $Hg_{18}S_{20}$ cannot form the necessary Hg–S–Hg bridges. We suggest that the CD signal arises from stacking of the Hg–S bonds in the protein either in a hairpin-like structure or in one that involves extensive coiling of the peptide chain. In the absence of aromatic amino acids, we only find exciton bands related to the Hg–S chromophore. Reports for both Cd_7-MT[10] and Co_7-MT[20] with EPR, CD, and MCD techniques support the view that metal-related transitions are reliable markers for the presence of well-defined, metal–thiolate structures.

Acknowledgment. We thank NSERC of Canada for financial support through a Strategic Grant and Drs. Zbigniew Gasyna and Andrzej Zelazowski for useful discussions. The authors are associated with the Centre for Chemical Physics and the Photochemistry Unit[21] at the UWO.

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(19) The evidence against dimer formation is as follows. There is no change in $\Delta\epsilon$ over a concentration range 1×10^{-6} to 2×10^{-5} M; Hg_{18}-MT forms preferentially at higher temperatures rather than at lower temperatures; the CD intensity arises from chiral $S \rightarrow Hg$ charge transfer transitions, not aligned peptide groups; we do not expect dimerization to result in well-defined chiral binding sites for the Hg; there is no free metal to induce dimerization; no disulfide bonds are present; Hg_{18}-MT elutes on the low mass side of cytochrome *c* on Sephadex 9-50.
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Enantioselective Synthesis of Dihydropyridine Sulfones[1]

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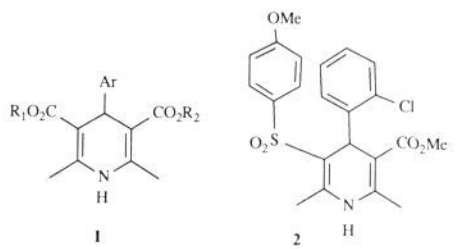
Received July 18, 1988

Calcium channel antagonistic 4-aryl-1,4-dihydropyridine-3,5-carboxylic acid diesters[2] (**1**) are important cardiovascular drugs



1 **2**

which inhibit smooth and cardiac muscle contractions by blocking the influx of calcium ions through plasma membrane channels.[3] When the two ester groups are different, C_4 of the dihydropyridine ring becomes chiral, and stereoselectivity of antagonism is observed.[4] Due to the many additional pitfalls which exist when assessing the pharmacological properties of racemic drugs[5] and the changing perception of this problem on the part of regulatory agencies, the preparation and biological evaluation of single isomers have become mandatory.

In the area of dihydropyridines (DHP), optically active isomers have been produced either by classical resolution of a monoacid or by separation of diastereomeric esters.[7] A potentially useful asymmetric synthesis of DHP derivatives involving enantioselective addition of organometallic reagents to the 4-position of a pyridine has been demonstrated in a simple case.[8]

Since we had identified the racemic sulfonyl DHP, **2**, as a potent, orally bioavailable and long acting antihypertensive agent in animal models, we decided to synthesize the corresponding

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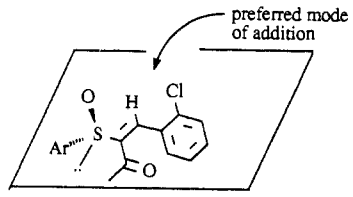
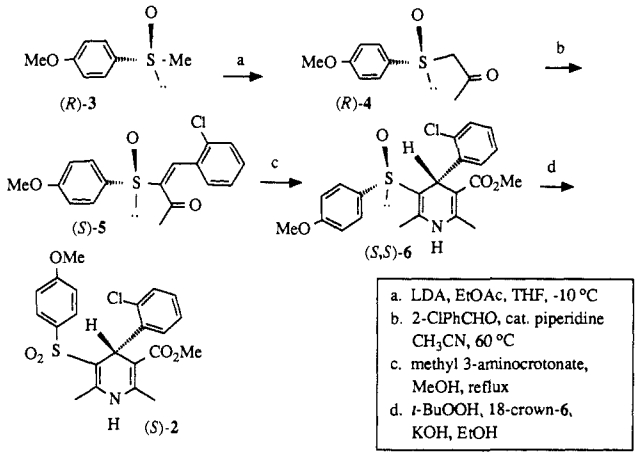


Figure 1. Addition of crotonate to (*S*)-**5**.

Scheme I



individual isomers. A successful strategy, which utilized an optically active sulfoxide as a transient stereogenic center, is described below (Scheme I).

Acylation (LDA, EtOAc, THF, −10 °C) of (*R*)-(+)-4-methoxymethyl methyl sulfoxide[9] (*R*)-**3** [>98% ee, $[\alpha]_D$ + 118°] gave the (*R*)-sulfinylpropanone (*R*)-**4** [mp 56–58 °C, $[\alpha]_D$ +168° (MeOH, *c* = 1), 76% yield],[10] which was condensed with 2-chlorobenzaldehyde under modified Knoevenagel conditions[11] (catalytic piperidine, CH_3CN, 60 °C) to provide exclusively the (*E*)-benzylidene (*S*)-**5** [mp 49–51 °C, $[\alpha]_D$ +184° (MeOH, *c* = 1), 74% yield]. Stereochemistry was established on the basis of ^1H NMR, literature precedence,[11] and the expectation that the (*E*)-benzylidene would be the more abundant isomer.[12] Hantzsch reaction (methyl 3-aminocrotonate, MeOH, reflux) of (*S*)-**5** gave the single diastereomer (*S,S*)-**6** [mp 175–177 °C, $[\alpha]_D$ +298° (MeOH, *c* = 1), 48% yield] as the result of an asymmetrically induced Michael addition, followed by dehydrative cyclization. Keto sulfoxide (*R*)-**3**, corresponding to 50% recovery (the result of H_2O-induced retro-Knoevenagel reaction), was the only other sulfoxide-containing material in the crude reaction mixture. In accordance with several literature precedents,[13] we propose that the addition of the crotonate occurs from the opposite side of the bulky methoxyphenylsulfinyl group to the preferred conformation of the sulfinylbenzylidene, in which the lone pair on sulfur and the chlorophenyl group are in an antiperiplanar arrangement (Figure 1). Such a conformation might also be favored by an electrostatic interaction between the lone pair on sulfur and the carbonyl group. Proof of the absolute stereochemistry of (*S,S*)-**6** was obtained by X-ray crystallography[14] (Figure 2).

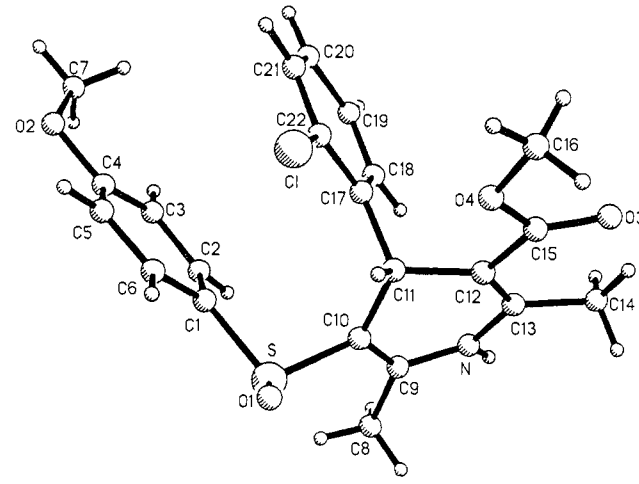
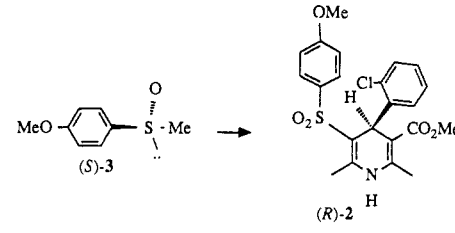


Figure 2. X-ray of (*S,S*)-**6**.

Scheme II



Having served its purpose as a stereogenic center, the sulfinyl function of (*S,S*)-**6** was oxidized[15] to the sulfone (*t*-BuOOH, 18-crown-6, KOH, EtOH) to give the target compound (*S*)-**2** [mp 197–200 °C, $[\alpha]_D$ +132° (MeOH, *c* = 1), 87% yield]. The optical purity of this material was determined to be 94.5% ee by shift reagent ^1H NMR[16] and chiral HPLC.[17]

The opposite isomer, (*R*)-**2**, was obtained similarly from (*S*)-(−)-4-methoxyphenyl methyl sulfoxide,[9] (*S*)-**3** (Scheme II), via (*S*)-**4** [mp 56–58 °C, $[\alpha]_D$ −169° (MeOH, *c* = 1] which was condensed with 2-chlorophenylbenzaldehyde by using traditional Knoevenagel conditions (NH_4OAc, PhH, Dean-Stark water separator). The resulting benzylidene (*R*)-**5**, as an *E*/*Z* mixture (~9:1), was directly subjected to the Hantzsch reaction (methyl 3-aminocrotonate, MeOH, reflux). The resulting diastereomer, (*R,R*)-**6** [mp 188–190 °C, $[\alpha]_D$ −297° (MeOH, *c* = 1), 37% yield] was readily separated chromatographically from the accompanying minor isomer derived from ((*Z*)-**5**). Oxidation of the sulfinyl function of (*R,R*)-**6** as described before furnished the desired sulfone (*R*)-**2** [mp 200–202 °C, $[\alpha]_D$ −137° (MeOH, *c* = 1), 98% ee, 89% yield].

In spontaneously hypertensive rats, (*S*)-**2** was about ten times as potent[18] in lowering blood pressure as (*R*)-**2**.

Acknowledgment. We thank Anton Michel and Kei-Ho Lee for the biological data.

Supplementary Material Available: Experimental procedures, ^1H NMR and combustion analysis data for representative compounds, and X-ray crystallographic data for (*S,S*)-**6** are provided (4 pages). Ordering information is given on any current masthead page.

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(10) All new compounds have been fully characterized spectrally, and elemental composition was established by combustion analysis.

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(16) Eu(hfc):compound molar ratio 1:6, $CDCl_3$.

(17) Pirkle covalent naphthylalanine column (250 × 4.6 mm), mobile phase 4% iPrOH/hexane, 1.5 mL/min, 254 nm UV detector.

(18) The medicinal chemistry of sulfonyl-substituted dihydropyridines will be reported subsequently.