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Studies on Novel and Chiral 1,4-Dihydropyridines. V.[1] Hantzsch-type 1,4-Dihydropyridines Having a Chiral Sulfinyl Group: Syntheses, Structures, and Biological Activity as a Calcium Channel Antagonist[2]

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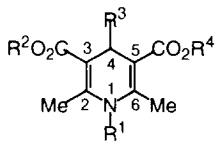
Abstract: 4-Aryl and 4-methyl substituted Hantzsch-type 1,4-dihydropyridines having a chiral sulfinyl group as an electron-withdrawing group were successfully synthesized in an optically active form from β-ketosulfoxides *via* two routes. The relationship between calcium channel antagonist activity and the structures of 4-aryl derivatives was also studied. © 1997 Elsevier Science Ltd.

Introduction

Generally, 2,6-dimethyl-1,4-dihydropyridines having two ester groups at C-3 and C-5, called Hantzsch esters (**1**),[3] have attracted much attention in the biological and chemical fields. From the biological viewpoint, these compounds are known to exhibit various significant biological activities such as a calcium channel antagonist,[4] an inhibitor of platelet aggregation and secretion,[5] and an ability to reverse drug resistance in a multidrug-resistant human carcinoma.[6] From the chemical viewpoint, it is known to work as a reducing agent as is obvious from its structure resembling that of NAD(P)H.[7] Recently, much interest is shown in such compounds having an electron-withdrawing group other than an ester group in view of their biological activities.[8]



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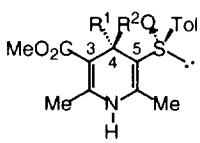

2Aa: R^1 = H, R^2 = Ph
b: R^1 = H, R^2 = *o*-ClC_6H_4
c: R^1 = H, R^2 = Me
2Ba: R^1 = Ph, R^2 = H
b: R^1 = *o*-ClC_6H_4, R^2 = H
c: R^1 = Me, R^2 = H

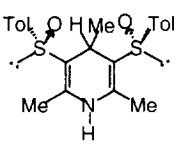

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Fig. 1

Our previous studies on 1-substituted 3-(*p*-tolylsulfinyl)-1,4-dihydropyridines as a chiral NADH model compound[1, 9] prompted us to investigate the chemical and biological properties of Hantzsch-type 1,4-dihydropyridines having a chiral sulfinyl group and an ester group at C-5 and C-3, respectively. We selected an aryl group (phenyl and *o*-chlorophenyl groups, **2a** and **2b**) as a 4-substituent since some 4-aryl substituted Hantzsch-type compounds are known to work as an effective calcium channel antagonist. In order to

investigate the reducing ability, 4-methyl derivatives **2c** were also synthesized since the aryl substituent at C-4 appeared to be too large to work as a reducing agent. Symmetrical compound **3** having two sulfinyl groups was also synthesized in view of our interest in its structural feature. In this paper, we report the details of our synthetic studies on these optically active Hantzsch-type compounds and also wish to describe the calcium channel antagonist activity of the 4-aryl derivatives **2a** and **2b**.

Syntheses of 4-Aryl and 4-Methyl Hantzsch-type Compounds

In order to obtain the two possible diastereoisomers **2A** and **2B** in an optically pure form, we planned to synthesize our target molecules **2** starting from **4**, which has a later 4-substituent in **2**, according to the three routes A-C shown in Fig. 2. In the routes A and C, two components (ammonia and an ester function) are coupled stepwise with the common sulfinyl function **4** in different sequences, while in the route B, **2** is directly synthesized by coupling two parts (sulfinyl part and ester part having an amino-group). Expecting different stereoselectivities, we first examined these routes A-C for the synthesis of 4-aryl derivatives **2a** and **2b**.

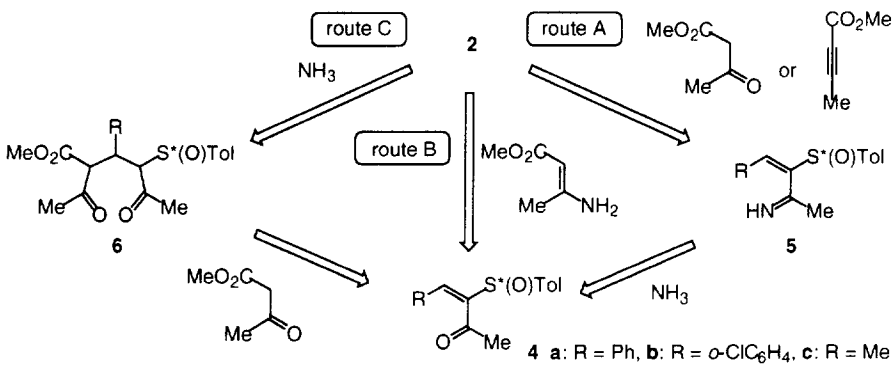
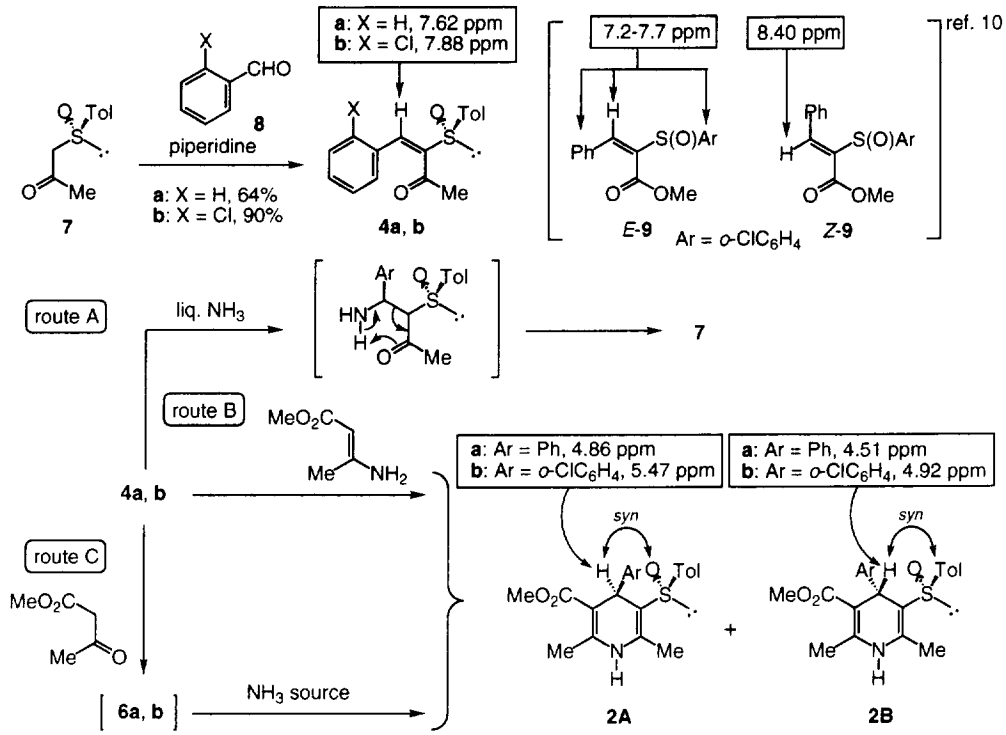


Fig. 2

The common starting materials **4a** and **4b** were easily obtained as a geometrically pure form by the modified Knoevenagel reaction[10] of the optically active α-sulfinylacetone **7**[11] with arylaldehydes **8a** and **8b**. As shown in Scheme 1, the geometry of olefins **4a** and **4b** was determined to be *E* by comparison of the chemical shift of the olefinic hydrogen with those of the related compounds **9** reported previously.[10] In the route A, several attempts to obtain iminosulfoxide **5** resulted in failure to afford the ketosulfoxide **7** as the main product, which is probably obtained by the Michael addition of ammonia to **4** and the following retro-aldol type reaction as shown in Scheme 1.

Although the route B was basically the same as that reported by Davis *et al.*,[8b] in our hands, the reaction under the same conditions (in MeOH under reflux) proceeded to give **2** only in low yield and low diastereoselectivity (Table 1, Runs 1 and 2). After several attempts, we eventually found that the isomer **2Aa** or **2Ab** was exclusively obtained in moderate yield when the reaction was carried out in 2,2,2-trifluoroethanol at room temperature and magnesium perchlorate was employed as a catalyst (Runs 3 and 4). These reaction conditions suggested to us that this reaction proceeded *via* a different transition state from that proposed by Davis *et al.*[8b] and shown in Fig. 3. Although the transition state chelating Mg^{2+} between the sulfinyl oxygen and the ketone is plausible,[12] it is supposed to afford the other isomer **2Ba** or **2Bb** (chelated transition state in



Scheme 1

Table 1. Syntheses of **2a** and **2b** by the routes B and C

Run	Route	Reagents and conditions	Compound **4**	Yield % (**2A** : **2B**)
1	B	methyl 3-aminocrotonate, MeOH, reflux	**a**	22% (3 : 2)
2			**b**	27% (3 : 2)
3	B	methyl 3-aminocrotonate, $Mg(ClO_4)_2$, CF_3CH_2OH, r.t.	**a**	55% (**2Aa** only)
4			**b**	45% (**2Ab** only)
5	C	1) methyl acetoacetate, NaH, THF, 0 °C	**a**	43% (2 : 3)
6		2) $AcONH_4$, MeOH, reflux	**b**	41% (1 : 2)

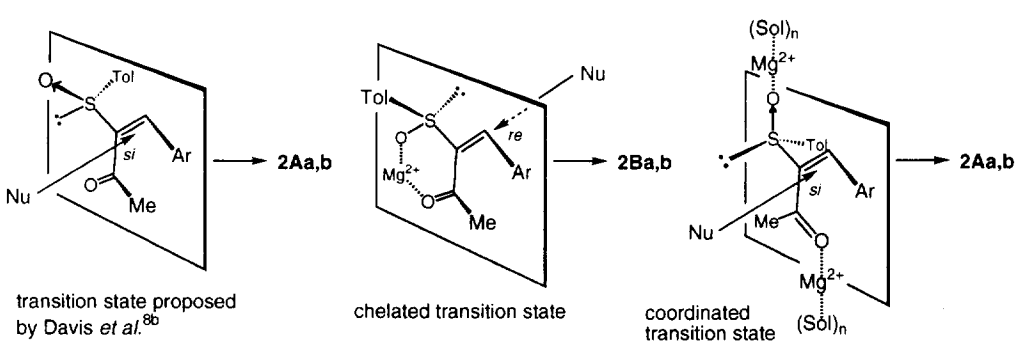


Fig. 3

Fig. 3). From the diastereoselectivity observed, it is obvious that this chelated transition state is not involved in this reaction. Taking into account diastereoselectivity obtained and the effects of magnesium salt and of the solvent, it is proposed the reaction under our conditions is most likely to proceed *via* the coordinated transition state shown in Fig. 3. This transition state may be rationalized in terms of allylic 1,3-strain[13] and dipole repulsion[14] between the sulfinyl group and the ketone. Coordination of magnesium with the sulfinyl oxygen and/or the carbonyl oxygen could restrict the conformation as shown and activate it as a Michael acceptor, making the reaction conditions milder as a result.

In the route C, reaction of ketosulfoxides **4a** and **4b** with methyl acetoacetate afforded diketones **6a** and **6b**, respectively, as a complex mixture of diastereomers. Without separation, diketones **6a** and **6b** were condensed with ammonium acetate to afford **2a** and **2b** as a mixture of diastereomers (Runs 5 and 6). In contrast to the route B, the **2B**-type isomers were predominantly obtained by this method.

The stereochemistries of these compounds **2Aa,b** and **2Ba,b** were assigned as shown in Scheme 1 by comparison of their ^{1}H NMR data and were alternatively confirmed by X-ray crystallographic analysis of **2Bb** as follows. ^{1}H NMR data of these compounds showed that, regardless of the substituent at C-4, the 4-hydrogens of **2A**-type isomers resonanced in lower field than did those of the corresponding **2B**-type isomers as shown in Scheme 1. This is attributable to the neighboring sulfinyl group, the conformation of which is thought to be restricted as shown in Scheme 1 to avoid an allylic 1,3-strain.[9b, 13] In this conformation, the 4-hydrogen of the **2A**-type isomers is close to the sulfinyl oxygen, while that of the **2B**-type isomers is above the plane of the tolyl group, thus these two isomers are clearly discriminated by ^{1}H NMR spectroscopy. X-ray crystallographic analysis of **2Bb** confirmed the conformation of the sulfinyl group as well as the structural assignments as shown in Fig. 4.

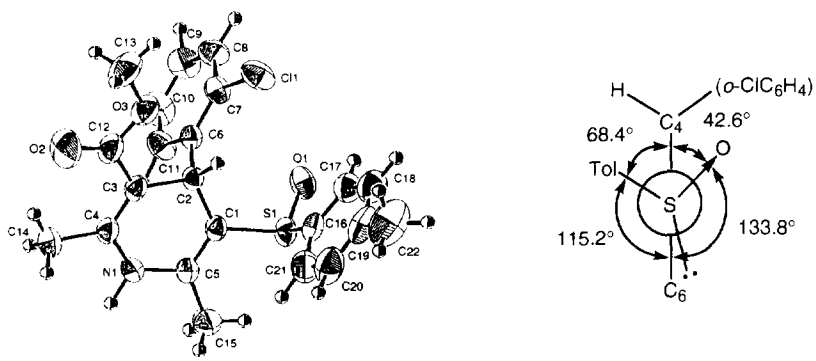
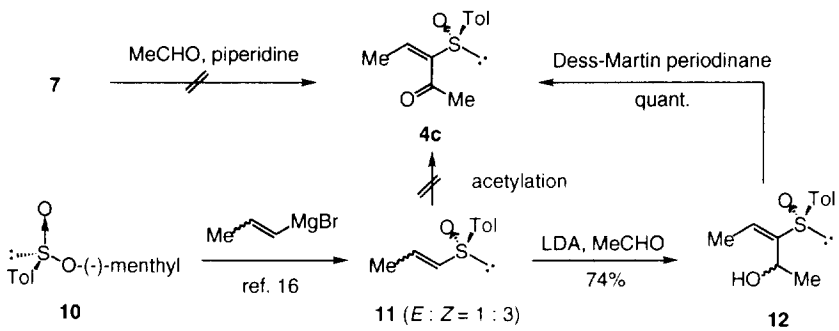


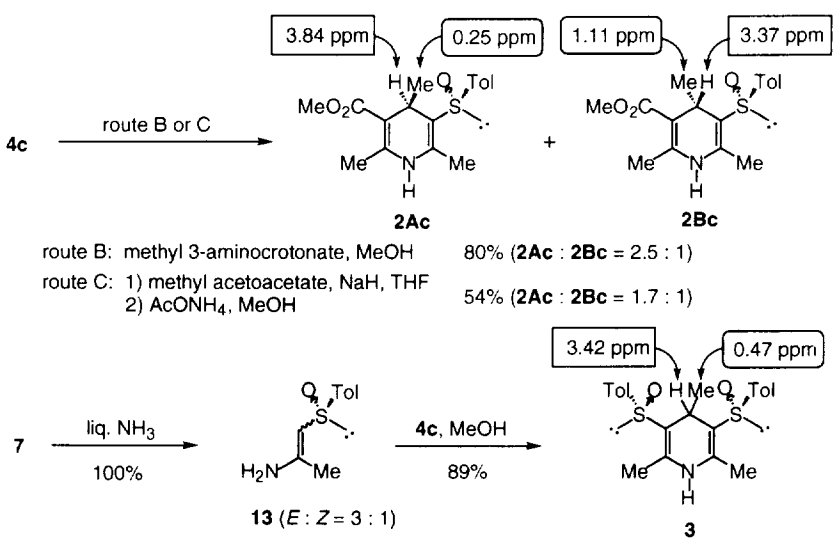
Fig. 4 ORTEP drawing of **2Bb** and conformation of the sulfinyl group observed in the crystalline state

In contrast to the 4-aryl derivatives **4a** and **4b**, synthesis of the ketosulfoxide **4c** was somewhat troublesome. Generally, the Knoevenagel reactions with enolizable aldehydes such as acetaldehyde are known to be less successful.[15] Indeed, the condensation of ketosulfoxide **7** with acetaldehyde was not achieved under similar conditions to those described for **4a** and **4b**. Hence, we have synthesized **4c** from vinyl sulfoxide **11** prepared by treatment of the optically pure sulfinate **10** with a Grignard reagent according to the literature[16] as shown in Scheme 2. The α-carbanions of vinyl sulfoxides were reported to be easily generated by treatment

with LDA.[17] Firstly, we examined the direct acetylation of the α-carbanion prepared from **11** by employing various acetylating agents such as ethyl acetate, acetic anhydride and acetyl halides. These attempts, however, resulted in failure to afford a complex mixture. In contrast, the reaction of **11** with acetaldehyde successfully proceeded accompanying the isomerization of the geometry of **11**[17b] to afford the *E*-alcohol **12** as a diastereomeric mixture (*ca.* 1 : 1). Although oxidation of this alcohol **12** had appeared to be carried out easily, the reactions with various oxidizing agents afforded unsatisfactory results. Finally, the Dess-Martin reagent[18] was found to be the choice for this oxidation and gave **4c** in quantitative yield. These difficulties encountered in the preparation of **4c** could be attributable to the fact that **4c** is a good Michael acceptor compared with **4a** and **4b**,[19] making the reaction product more complex and the isolation from the reaction mixture difficult.



Scheme 2



Scheme 3

Next, we applied the routes B and C to the synthesis of 4-methyl derivatives **2Ac** and **2Bc** from **4c** (Scheme 3). In contrast to the case of 4-aryl derivatives, the reaction of **4c** with 3-aminocrotonate catalyzed by magnesium salt in 2,2,2-trifluoroethanol only afforded a complex mixture, while that without magnesium salt in methanol afforded **2Ac** as the major product in good yield. Although the reaction according to the route C also took place to give a moderate yield, the diastereoselectivitiy obtained was similar to that of the route B.

Bissulfinyl derivative **3** was obtained by the route B as follows (Scheme 3). Treatment of **7** with liquid ammonia in a sealed tube gave enamine **13** as an unstable mixture of geometric isomers in quantitative yield. Without further purification, **13** was reacted with **4c** to afford the desired product **3**. In spite of our efforts, the diketone corresponding to **6** was not obtained from **4c** and **7** at all under the conditions for the route C.

The stereochemistries of **2Ac** and **2Bc** were confirmed by comparison of ^{1}H NMR data with those of 4-aryl derivatives. Similar to those of the 4-aryl derivatives, the hydrogen and the methyl group at C-4 of **2Ac** and **2Bc** are characteristically discriminated from each other by the effects of the sulfinyl oxygen and the tolyl group, respectively. On the other hand, the chemical shifts for the hydrogen and the methyl group at C-4 of **3** are observed in the range of those for **2Ac** and **2Bc** as shown in Scheme 3. This is attributable to the fact that these substituents (the methyl group and hydrogen) at C-4 of **3** are affected by both the sulfinyl oxygen and the tolyl group.

Relation between Calcium Channel Antagonist Activities and Structures of 4-Aryl Derivatives

The activities of 4-aryl derivatives **2Aa,b** and **2Ba,b** were assayed by measuring the vasorelaxant activity using the mescenteric artery enucleated from a rat[20] and were evaluated by comparison with that of nifedipine, an effective and clinically employed calcium channel antagonist (Table 2). Concerning the substituent at C-4, *o*-chlorophenyl derivatives **2Ab** and **2Bb** were shown to be more effective than the respective phenyl derivatives **2Aa** and **2Ba** (**2Aa** vs. **2Ab** and **2Ba** vs. **2Bb**) as is generally known.[4]

Table 2. Vasorelaxant activity of nifedipine and sulfinylated Hantzsch-type compounds **2**

Compd.	Conc. (nM)	Relative Activity (%)
nifedipine	1	100
2Aa	10	10
2Ba	1	24
2Ba	10	69
2Ab	10	29
2Bb	1	50
2Bb	0.1	8

Interestingly, regardless of the substituent at C-4, **2B**-type isomers were more active than **2A**-type isomers (**2Aa** vs. **2Ba** and **2Ab** vs. **2Bb**). Totally, compound **2Bb** satisfying both structural and stereochemical requirements was the best among these compounds **2** and its activity was *ca.* 1/2 of that of nifedipine.

In general, the following structural and conformational features of typical Hantzsch-type compounds have been revealed to be requisite for an effective calcium channel antagonist (Fig. 5-A).[4c] 1) Unsymmetrical compounds generally tend to be more active than symmetrical ones. 2) When the ester substituent R^2 is larger than R^1 and is put over the ester group R^1 as shown in Fig. 5-A, the 4-aryl substituent should be positioned in the β-orientation and simultaneously should occupy the pseudo-axial position. 3) The 1,4-dihydropyridine ring should have a boat form. 4) The relation between the hydrogen at C-4 and the *o*- or *m*-substituent on the phenyl group at C-4 should be *syn*-periplanar. 5) At least one of the two ester carbonyl groups should be in the *syn*-arrangement with the C_2-C_3 double bond of the 1,4-dihydropyridine ring (i.e., the C_3-C=O bond should be s-*cis*).

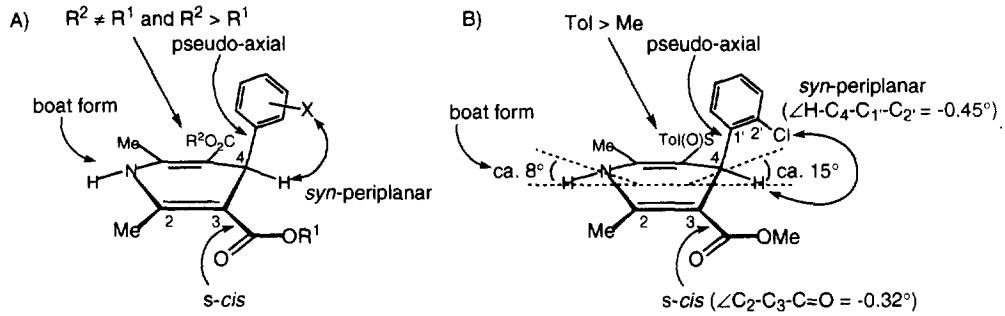


Fig. 5 A) Structural and conformational requirements to work as an effective calcium channel antagonist and B) structural and conformational characters of **2Bb** obtained by X-ray analysis

As described above, X-ray crystallographic analysis revealed that **2Bb** has a conformational character in the crystalline state as shown in Fig. 5-B. If the sulfinyl group is taken as an equivalent for a large ester group (R^2O_2C in Fig. 5-A),[21] **2Bb** having the conformation (Fig. 5-B) would best satisfy the required factors (Fig. 5-A).[22] This could explain the result of the biological assay in which **2Bb** is the most potent antagonist.

These findings show not only that the Hantzsch-type compounds having a sulfinyl group in place of an ester group also exhibit calcium channel antagonist activity, but also that the general structure-activity relationship reported for those having two ester groups can be applied to those having a sulfinyl group.

Experimental

General. All melting points (mps) were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-200 spectrometer. ^{1}H NMR spectra were measured on a JEOL GX-500 (500 MHz), Hitachi R-250HT (250 MHz), or a Varian VXR-200 (200 MHz) spectrometer and tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were measured on a JEOL EX-270 (68 MHz) with $CDCl_3$ or DMSO-d_6 as an internal standard (77.0 ppm or 39.5 ppm). Low and High resolution mass spectra (MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer. For silica gel column chromatography, E. Merck Kieselgel 60 (0.063-0.200 mm) was used.

(S_S)-(*E*)-1-Phenyl-2-(*p*-tolylsulfinyl)-1-buten-3-one (4a) To a stirred solution of (S_S)-1-(*p*-tolylsulfinyl)-2-propanone (**7**, 2.00 g, 10.2 mmol) and piperidine (99.0 mg, 1.2 mmol) in acetonitrile (40 ml) was added benzaldehyde (1.55 ml, 15.3 mmol) at room temperature. The reaction mixture was refluxed for 5 h and then the solvent was evaporated off. The residue was chromatographed on silica gel with hexane-AcOEt (2:1) to give **4a** (1.85 g, 64%) as colorless needles, mp 123-124 °C (hexane). $[\alpha]_D^{23}$ +359° (*c* 1.39, $CHCl_3$). IR ν_{max} ($CHCl_3$): 1675, 1360, 1080, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.79 (3H, s, MeCO), 2.39 (3H, s, Ar-Me), 7.28, 7.57 (4H, AA'BB', *J* = 8 Hz, aromatic), 7.32-7.41 (5H, m, aromatic), 7.62 (1H, s, =CHPh). ^{13}C NMR ($CDCl_3$) δ_C: 21.48, 30.87, 125.75, 128.88, 129.18, 129.94, 130.03, 133.44, 135.15, 139.19, 142.43, 147.12, 199.82. MS (EI) *m/z*: 284 (M^+, 4), 236 (54), 140 (69), 92 (100). *Anal.* Calcd for $C_{17}H_{16}O_2S \cdot 1/8H_2O$: C, 71.24; H, 5.71; S, 11.19. Found: C, 71.30; H, 5.46; S, 11.03.

(S_S)-(*E*)-1-(*o*-Chlorophenyl)-2-(*p*-tolylsulfinyl)-1-buten-3-one (4b) In a similar fashion to that described for **4a**, treatment of **7** (2.00 g, 10.2 mmol) with *o*-chlorobenzaldehyde (1.72 ml, 15.3 mmol) and piperidine (99 mg, 1.2 mmol) gave **4b** (2.94 g, 90%) as colorless needles, mp 134-135 °C (hexane). $[\alpha]_D^{23}$ +401° (*c* 1.05, $CHCl_3$). IR ν_{max} ($CHCl_3$): 1675, 1350, 1070, 1040 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.70 (3H, s,

MeCO), 2.39 (3H, s, Ar-Me), 7.20-7.63 (8H, m, aromatic), 7.88 (1H, s, =CHPh). ^{13}C NMR ($CDCl_3$) δ_C: 21.48, 30.53, 125.95, 127.06, 129.99, 130.06, 130.33, 130.84, 132.69, 133.39, 133.48, 139.32, 142.48, 149.24, 198.45. MS (EI) *m/z*: 318 (M^+, 5), 235 (93), 140 (100), 92 (99). *Anal.* Calcd for $C_{17}H_{15}ClO_2S \cdot 1/8H_2O$: C, 63.59; H, 4.80; S, 9.98; Cl, 11.06. Found: C, 63.72; H, 4.57; S, 9.95; Cl, 10.99.

Methyl (4*R*,S_S)- and (4*S*,S_S)-1,4-Dihydro-2,6-dimethyl-4-phenyl-5-(*p*-tolylsulfinyl)-pyridine-3-carboxylate (2Aa and 2Ba)

Route B in MeOH Under a nitrogen atmosphere, a solution of **4a** (200 mg, 0.704 mmol) and methyl 3-aminocrotonate (89.1 mg, 0.774 mmol) in MeOH (15 ml) was stirred and refluxed for 24 h. After cooling, the solvent was evaporated off under reduced pressure and the resultant residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (2:1) to afford **2Aa** (37 mg, 13%) and **2Ba** (23 mg, 9%) as colorless crystals, respectively. **2Aa**, mp 212-213 °C (MeOH). $[\alpha]_D^{22}$ +140° (*c* 0.54, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3450, 1690, 1650, 1620, 1070, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.19, 2.29 (each 3H, each s, 2- and 6-Me), 2.44 (3H, s, Ar-Me), 3.57 (3H, s, CO_2Me), 4.86 (1H, s, 4-H), 5.73 (1H, br s, NH) , 6.72-7.07 (9H, m, aromatic). ^{13}C NMR (DMSO-d_6) δ_C: 15.89, 18.48, 20.67, 33.70, 50.59, 102.10, 113.77, 124.08, 124.94, 126.94, 127.24, 128.63, 139.09, 139.68, 141.92, 146.22, 146.88, 167.12. MS (EI) *m/z*: 381 (M^+, 0.5), 364 (100). *Anal.* Calcd for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.07; N, 3.67; S, 8.40. Found: C, 69.16; H, 6.13; N, 3.65; S, 8.34. **2Ba**, mp 176-177 °C (benzene-hexane). $[\alpha]_D^{21}$ +518° (*c* 0.63, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3450, 1690, 1650, 1620, 1075, 1005 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.23, 2.30 (each 3H, each s, 2- and 6-Me), 2.40 (3H, s, Ar-Me), 3.47 (3H, s, CO_2Me), 4.51 (1H, s, 4-H), 6.56 (1H, br s, NH), 7.10-7.43 (9H, m, aromatic). ^{13}C NMR (DMSO-d_6) δ_C: 16.01, 18.48, 20.94, 36.52, 50.66, 101.22, 114.38, 124.53, 125.91, 127.19, 127.89, 129.56, 139.98, 141.15, 141.40, 145.90, 147.49, 167.10. MS (EI) *m/z*: 381 (M^+, 0.6), 363 (100). *Anal.* Calcd for $C_{22}H_{23}NO_3S$: C, 69.26; H, 6.07; N, 3.67; S, 8.40. Found: C, 69.15; H, 6.11; N, 3.60; S, 8.24.

Route B with $Mg(ClO_4)_2$ in 2,2,2-trifluoroethanol To a stirred solution of **4a** (100 mg, 0.352 mmol) in 2,2,2-trifluoroethanol (1.8 ml) was added magnesium perchlorate (39.3 mg, 0.176 mmol) at room temperature. After 10 min, a solution of methyl 3-aminocrotonate (40.5 mg, 0.352 mmol) in 2,2,2-trifluoroethanol (0.5 ml) was added and the reaction mixture was stirred for 3 h at room temperature. After addition of water, the mixture was extracted with $CHCl_3$ and the organic layer was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (2:1) to give **2Aa** (73 mg, 55%) as colorless crystals.

Route C To a stirred suspension of sodium hydride (60% in oil, 42 mg, 1.05 mmol) in THF (20 ml) was added methyl acetoacetate (1.13 ml, 10.6 mmol) at 0 °C under a nitrogen atmosphere and the whole was stirred for 10 min at the same temperature. A solution of **4a** (1.50 g, 5.28 mmol) in THF (20 ml) was added to the reaction mixture and stirring was continued further for 1 h at 0 °C. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water, brine, dried and concentrated to afford a diastereomeric mixture of diketones **6a**, which was immediately used for the next step without further purification. To a solution of **6a** in MeOH (30 ml) was added ammonium acetate (1.04 g, 13.5 mmol) and the reaction mixture was refluxed for 1 h. After evaporation of almost all the solvent, the residue was extracted with water and CH_2Cl_2 and the combined organic layer was washed with brine, dried and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (2:1) to give **2Aa** (297 mg, 17%) and **2Ba** (440 mg, 26%) as colorless crystals, respectively.

Methyl (4*S*,S_S)- and (4*R*,S_S)-4-(*o*-Chlorophenyl)-1,4-dihydro-2,6-dimethyl-5-(*p*-tolylsulfinyl)pyridine-3-carboxylate (2Ab and 2Bb) Compound **4b** was treated according to similar

procedures (routes B and C) to those described for the preparation of 4-phenyl derivatives **2a**. The results are summarized in Table 1 and physical properties of **2Ab** and **2Bb** are as follows. **2Ab**, colorless crystals, mp 199-200 °C (MeOH). $[\alpha]_D^{22}$ +141° (*c* 0.51, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3450, 1690, 1655, 1620, 1075, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.17, 2.31 (each 3H, each s, 2- and 6-Me), 2.39 (3H, s, Ar-Me), 3.53 (3H, s, CO_2Me), 5.47 (1H, s, 4-H), 6.68-7.17 (9H, m, NH and aromatic). ^{13}C NMR (DMSO-d_6) δ_C: 16.21, 18.24, 20.65, 31.18, 50.37, 101.15, 113.44, 123.87, 126.76, 126.88, 128.30, 128.56, 130.82 (2C), 138.64, 139.16, 142.00, 144.55, 146.40, 167.17. MS (EI) *m/z*: 415 (M^+, 0.5), 139 (100). *Anal.* Calcd for $C_{22}H_{22}ClNO_3 \cdot 3/4H_2O$: C, 61.53; H, 5.52; N, 3.26; S, 7.46; Cl, 8.27. Found: C, 61.80; H, 5.81; N, 3.24; S, 7.35; Cl, 8.12. **2Bb**, colorless crystals, mp 139-141 °C (AcOEt). $[\alpha]_D^{22}$ +464° (*c* 0.64, $CHCl_3$). IR ν_{max} ($CHCl_3$): 3450, 1690, 1655, 1620, 1075, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.18, 2.25 (each 3H, each s, 2- and 6-Me), 2.42 (3H, s, Ar-Me), 3.46 (3H, s, CO_2Me), 4.92 (1H, s, 4-H), 6.95-7.51 (9H, m, NH and aromatic). ^{13}C NMR (DMSO-d_6) δ_C: 16.18, 18.21, 20.83, 34.36, 50.30, 101.57, 115.35, 124.62, 127.10, 128.63, 129.36, 130.15, 130.82 (2C), 139.68, 140.72, 140.88, 145.46, 147.08, 166.87. MS (EI) *m/z*: 398 (M^+-OH, 5), 240 (100). *Anal.* Calcd for $C_{22}H_{22}ClNO_3 \cdot 1/2H_2O$: C, 62.18; H, 5.46; N, 3.30; S, 7.54; Cl, 8.35. Found: C, 62.06; H, 5.33; N, 3.36; S, 7.35; Cl, 8.52.

X-Ray Crystallographic Analysis of 2Bb Because of its crystal form, we used a crystal of (±)-**2Bb**, which had been synthesized from (±)-**4b** according to the route C, for X-ray analysis. Crystal data and data collections are as follows. Empirical formula: $C_{22}H_{22}ClNO_3S$, Formula weight: 415.93, Crystal system: monoclinic, Space group: $P2_1/n$, Cell constant: a = 11.153(2) Å, b = 22.783(3) Å, c = 8.416(5) Å, β = 94.37(3)°, V = 2132(2) $Å^3$, Z: 4, F(000): 872, Crystal dimensions: 0.25 × 0.4 × 0.3 mm, μ(Mo-K_α): 2.92 cm^{-1}. Diffractometer: Rigaku AFC5R, Radiation: Mo-K_α, Temperature: 23 °C, Scan type: ω - 2θ, Scan rate: 32.0°/min (in ω), Scan width: (1.50 + 0.30 tan θ)°, $2\theta_{max}$: 55.0°, No. of the unique reflections measured: 5032. Refinement: Full-matrix least-squares, No. of observations: 2481 ($I > 3\sigma(I)$), No. of variables: 253, Residuals: R, 0.049; R_w, 0.056.

(2*R*,S_S)- and (2*S*,S_S)-(*E*)-3-(*p*-Tolylsulfinyl)-3-penten-2-ol (12) A solution of **11** (*E* : *Z* = *ca.* 1:3, 5.00 g, 27.8 mmol) in THF (30 ml) was added dropwise to a stirred solution of LDA [41.7 mmol, prepared from diisopropylamine (5.84 ml, 41.7 mmol) and *n*-butyllithium in hexane (1.6 M, 26.1 ml, 41.7 mmol)] in THF (240 ml) at -78 °C and stirring was continued at the same temperature for 30 min. A THF solution of acetaldehyde (5.6 M, 15 ml, 84 mmol) was added dropwise to the above reaction mixture at -78 °C and the whole was stirred for 1.5 h at the same temperature. After addition of saturated aq. $NaHCO_3$, the mixture was extracted with AcOEt and the organic layer was washed with water, brine, dried and concentrated. The resulting residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (1:2) to give less polar **12** (2.30 g, 37%) and more polar **12** (2.30 g, 37%) as colorless crystals, respectively. Less polar **12**, mp 113-114 °C (Et_2O). $[\alpha]_D^{22}$ +82° (*c* 0.99, acetone). IR ν_{max} ($CHCl_3$): 3400, 1070, 1020, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (3H, d, *J* = 7 Hz, CH(OH)*Me*), 1.98 (3H, d, *J* = 7 Hz, =CH*Me*), 2.40 (3H, s, Ar-Me), 2.40 (1H, br s, OH), 4.68 (1H, q, *J* = 7 Hz, C*H*(OH)Me), 6.45 (1H, q, *J* = 7 Hz, =C*H*Me), 7.29, 7.50 (4H, AA'BB', *J* = 6 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 14.25, 21.35, 23.02, 65.91, 125.14, 129.81, 132.63, 140.27, 141.29, 146.76. MS (EI) *m/z*: 224 (M^+, 6), 140 (79), 92 (100). *Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.26; H, 7.18; S, 14.06. More polar **12**, mp 99-100 °C (Et_2O). $[\alpha]_D^{23}$ +71° (*c* 1.12, acetone). IR ν_{max} ($CHCl_3$): 3400, 1070, 1020, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.22 (3H, d, *J* = 7 Hz, CH(OH)*Me*), 1.97 (3H, d, *J* = 7 Hz, =CH*Me*), 2.40 (3H, s, Ar-Me), 2.78 (1H, br s, OH), 4.77 (1H, q, *J* = 7 Hz, C*H*(OH)Me), 6.52 (1H, q, *J* = 7 Hz, =C*H*Me), 7.29, 7.53 (4H, AA'BB', *J* = 8 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 14.47, 21.35, 22.84, 63.97, 125.16, 129.76, 132.29, 139.80, 141.28, 148.19. MS (EI) *m/z*:

224 (M^+, 7), 140 (88), 92 (100). *Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.13; H, 7.16; S, 14.04.

(S_S)-(*E*)-3-(*p*-Tolylsulfinyl)-3-penten-2-one (4c) To a solution of **12** (908 mg, 4.05 mmol) in CH_2Cl_2 (33 ml) was added Dess-Martin periodinane[18] (1.89 g, 4.46 mmol) and the reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was diluted with ether, and then stirred with a mixture of saturated aq. $NaHCO_3$ and aq. $Na_2S_2O_3$ for 10 min. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with water, brine, dried and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (1:2) to give **4c** (891 mg, 100%) as colorless crystals, mp 60-61 °C (Et_2O). $[\alpha]_D^{24}$ +238° (*c* 1.07, acetone). IR ν_{max} ($CHCl_3$): 2995, 1690, 1660, 1625, 1595, 1075, 1020, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.21 (3H, d, *J* = 8 Hz, =CH*Me*), 2.24 (3H, s, COMe), 2.38 (3H, s, Ar-Me), 7.05 (1H, q, *J* = 8 Hz, =C*H*Me), 7.25, 7.51 (4H, AA'BB', *J* = 8 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 15.80, 21.37, 31.41, 125.66, 129.85, 139.46, 140.13, 141.87, 146.27, 195.96. MS (EI) *m/z*: 222 (M^+, 19), 139 (73), 92 (100). *Anal.* Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.34; S, 14.42. Found: C, 64.67; H, 6.37; S, 14.37.

Methyl (4*R*,S_S)- and (4*S*,S_S)-1,4-Dihydro-2,4,6-trimethyl-5-(*p*-tolylsulfinyl)pyridine-3-carboxylate (2Ac and 2Bc)

Route B To a stirred solution of **4c** (500 mg, 2.25 mmol) in MeOH (30 ml) was added a solution of methyl 3-aminocrotonate (283 mg, 2.42 mmol) in MeOH (5 ml) at 0 °C and the reaction mixture was stirred at room temperature for 24 h. After concentration, the resulting crystalline residue was collected by filtration and washed with AcOEt to give **2Ac** (280 mg, 40%) as colorless crystals. The filtrate was concentrated and the resulting residue was chromatographed on silica gel with CH_2Cl_2-AcOEt (1:2) to give **2Ac** (120 mg, 17%, total 400 mg, 57%) and **2Bc** (172 mg, 23%) as colorless crystals, respectively. **2Ac**, mp 186-187 °C ($CHCl_3$-Et_2O). $[\alpha]_D^{22}$ +543° (*c* 1.03, MeOH). IR ν_{max} ($CHCl_3$): 3450, 2980, 1695, 1650, 1620, 1095 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.25 (3H, d, *J* = 6 Hz, 4-Me), 2.25 (3H, s, 2-Me), 2.31 (3H, s, 6-Me), 2.39 (3H, s, Ar-Me), 3.65 (3H, s, CO_2Me), 3.83 (1H, q, *J* = 6 Hz, 4-H), 7.21 (1H, br s, NH), 7.28, 7.51 (4H, AA'BB', *J* = 8 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 16.34, 18.89, 21.21, 21.60, 23.33, 50.77, 103.49, 115.58, 124.28, 129.58, 140.49, 140.95, 141.76, 147.04, 167.76. MS (EI) *m/z*: 319 (M^+, 1), 304 (100). *Anal.* Calcd for $C_{17}H_{21}NO_3S \cdot 1/5H_2O$: C, 63.21; H, 6.68; N, 4.34; S, 9.92. Found: C, 63.21; H, 6.55 N, 4.42; S, 10.21. **2Bc**, mp 173-174 °C (AcOEt). $[\alpha]_D^{22}$ +480° (*c* 1.04, MeOH). IR ν_{max} ($CHCl_3$): 3450, 2980, 1695, 1655, 1620, 1095 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.11 (3H, d, *J* = 7 Hz, 4-Me), 2.25 (3H, s, 2-Me), 2.33 (3H, s, 6-Me), 2.38 (3H, s, Ar-Me), 3.37 (1H, q, *J* = 7 Hz, 4-H), 6.75 (1H, br s, NH), 7.25, 7.43 (4H, AA'BB', *J* = 8 Hz, aromatic). ^{13}C NMR ($CDCl_3$) δ_C: 16.44, 19.18, 21.26, 24.57, 27.12, 50.77, 103.99, 116.66, 124.71, 129.47, 140.13, 140.18, 140.27, 145.16, 167.76. MS (EI) *m/z*: 304 (M^+-Me, 49), 302 (33), 83 (100). *Anal.* Calcd for $C_{17}H_{21}NO_3S \cdot 1/10H_2O$: C, 63.56; H, 6.65; N, 4.36; S, 9.98. Found: C, 63.55; H, 6.67; N, 4.15; S, 9.81.

Route C Reaction was carried out according to a similar procedure to that described for the 4-aryl derivative **2a**. The results are shown in Scheme 3.

(S_S)-2-Amino-1-(*p*-tolylsulfinyl)-2-propene (13) A solution of **7** (200 mg, 1.02 mmol) in liq. NH_3 (5 ml) was stirred in a sealed tube for 24 h at room temperature. The reaction mixture was concentrated at room temperature to give the enamine **13** (198 mg, 100%, *E* : *Z* = *ca.* 3:1) as a white solid. IR ν_{max} ($CHCl_3$): 3450, 2950, 1625, 1585, 990 cm^{-1}. ^1H NMR (DMSO-d_6) δ: *E*-isomer: 2.09 (3H, s, C=C-Me), 2.34 (3H, s, Ar-Me), 4.92 (1H, s, C=C-H), 6.18 (2H, br s, NH_2), 7.29, 7.39 (4H, AA'BB', *J* = 8 Hz, aromatic). *Z*-isomer:

1.79 (3H, s, C=C-Me), 2.38 (3H, s, Ar-Me), 4.57 (1H, s, C=C-H), 6.23 (2H. br s, NH_2), 7.29, 7.39 (4H, AA'BB', J = 8 Hz, aromatic). ^{13}C NMR (DMSO-d_6) δ_C: *E*-isomer: 16.64, 20.72, 99.39, 124.03, 129.22, 138.73, 145.43, 156.23. *Z*-isomer: 16.64, 21.80, 95.69, 123.96, 129.29, 139.01, 144.53, 154.23. MS (EI) *m/z*: 195 (M^+, 1), 147 (100). HR-MS Calcd for $C_{10}H_{13}NOS$ *m/z*: 195.0716. Found 195.0716, which was used in the next step without further purification.

(S_S,$S_{S'}$)-1,4-Dihydro-2,4,6-trimethyl-3,5-bis(*p*-tolylsulfinyl)pyridine (3) To a stirred solution of **4c** (180 mg, 0.81 mmol) in MeOH (5 ml) was added a solution of **13** (175 mg, 0.90 mmol) in MeOH (5 ml) at 0 °C under a nitrogen atmosphere. Stirring was continued for 36 h and the solvent was evaporated off. The residue was chromatographed on silica gel (AcOEt) to give **3** (289 mg, 89%) as colorless crystals, mp 166-167 °C (AcOEt). $[\alpha]_D^{24}$ +717° (*c* 0.51, $CHCl_3$). IR ν_{max} (KBr): 3207, 1646, 1491, 1269, 1080, 1010, 807 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.47 (3H, d, J = 7 Hz, 4-Me), 2.20, 2.23 (each 3H, each s, 2- and 6-Me), 2.36, 2.42 (each 3H, each s, Ar-Me), 3.42 (1H, q, J = 7 Hz, 4-H), 7.19, 7.26 (4H, AA'BB', J = 8 Hz, aromatic), 7.31, 7.45 (4H, AA'BB', J = 8 Hz, aromatic), 7.60 (1H, br s, NH). ^{13}C NMR ($CDCl_3$) δ_C: 16.32, 16.35, 21.28, 21.40, 23.49, 24.21, 114.70, 115.58, 124.24, 125.09, 129.56, 129.63, 139.26, 140.47, 140.59, 140.72, 141.26, 142.07. MS (EI) *m/z*: 399 (M^+, 0.2), 242 (100). *Anal.* Calcd for $C_{22}H_{25}NO_2S_2 \cdot 1/4H_2O$: C, 65.39; H, 6.36; N, 3.47; S, 15.85. Found: C, 65.51; H, 6.28; N, 3.54; S, 15.80.

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19. Owing to the steric repulsion between the benzene ring and the acetyl group of **4a** and **4b**, these two groups are not thought to conjugate with the double bond sufficiently. Consequently, this would make **4a** and **4b** less effective Michael acceptors than **4c**.

20. The mescenteric artery enucleated from a rat was perfused with a Tyrode solution containing KCl (70 mM) and the high perfusion state was maintained. To the perfusion solution, a DMSO solution of the sample was added and the vasorelaxation was evaluated by measuring the perfusion pressure.

21. Taking into account the electron-withdrawing property and ability to work as a hydrogen-bond acceptor, the sulfinyl group of **2** could act as a conformationally restricted ester group. We already reported the effective NADH model compound having a sulfinyl group in place of an amide group.[1,9]

22. Although the conformation in the solution state is not clear, it would appear to be different from that in the crystalline state in some respects. However, it is obvious that this difference in conformation between the solution state and the crystalline state would not be a problem compared with the structural and stereochemical differences (i.e., **2Bb** vs. **2Ba** and **2Bb** vs. **2Ab** in Table 2).

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