Crystal Structure of Crotonic Acid Ester of the Highly Potent Chiral Auxiliary *trans*-2-[1-(2-Naphthyl)-1-methylethyl]-cyclohexanol: A Direct Evidence for the Critical Participation of Intramolecular π-Stacking Interaction in a Diastereofacial Differentiation Process

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Presence of a pendant aromatic nucleus is a salient feature common to many chiral auxiliaries, particularly those which provide the highest levels of stereocontrol. Pertinent examples of such auxiliaries are given by 8-arylmenthols **1**,[1] *trans*-2-arylcyclohexanols **2**,[1d,2] alcohols **3**[3] derived from β-pinene, and 1-phenylethylamine **4**.[4]

The purpose of this paper is to report the crystal structure of crotonate **10**, derived from the chiral auxiliary **9**, bearing a naphthalene nucleus. *This shows that the two π-systems of the present molecule are engaged in a stacked geometry* (Figure 1), a phenomenon consistent with the outstanding π-facial selectivity observed in the conjugate addition of diphenylmethaneamine to this crotonate [**10** → **11**] (Scheme 2).

It is manifest that the aromatic part of the aforementioned chiral inducers plays a crucial role in the asymmetric processes in which they are implicated, by increasing (or even being at the origin of) the observed directing effects. Among the hypotheses inspired for the critical participation of an aromatic ring in diastereomeric transition states, the stabilization by π-stacking interaction has emerged as one of the most attractive explanations.[5] However, although the intermolecular through-space π−π overlap is undeniably involved in diverse fundamental phenomena, such as the stabilization of the double helical structure of DNA, the tertiary structure of proteins, and others,[6] to date there are only very few indisputable evidences for the participation of such an interaction in controlling the stereoselectivity of organic processes.[7]

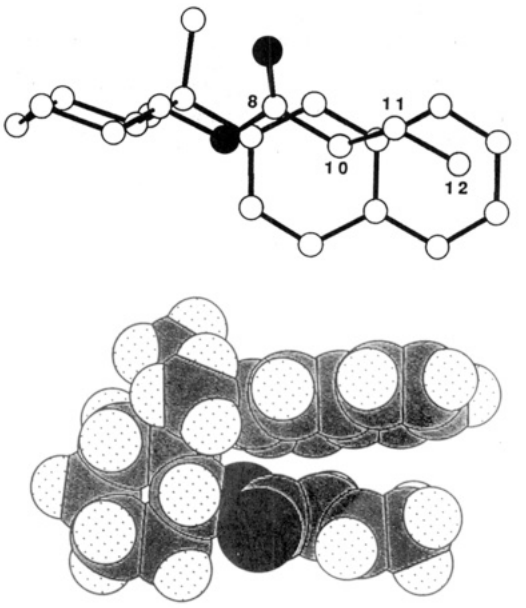
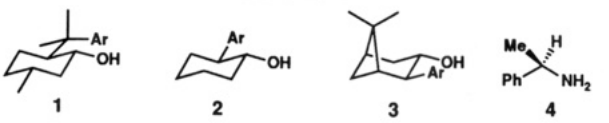
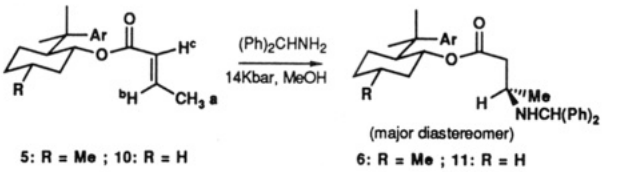


Figure 1. (Top) plot of the X-ray crystal structure of crotonate **10**, viewing the molecule perpendicularly to the naphthalene plane (hydrogen atoms are omitted). (Bottom) space-filling diagram concentrating on the π-system region.

Scheme 1



Scheme 2



R	Ar	^{1}H NMR of starting crotonates δ ppm Ha	Hb	Hc	de % in Michael adducts
Me	H	1.78	6.96	5.83	10
Me	Ph	1.72	6.44	5.32	60
Me	β-naphthyl	1.23	6.07	4.92	99
H	β-naphthyl	1.15	6.06	4.93	98

A convincing experimental support of the existence of an intramolecular π-stacking interaction in 8-arylmenthyl crotonates **5**, derived from alcohols **1**, is furnished by their ^{1}H NMR analysis (Scheme 2).[1c,8] We have indeed established that the protons of the crotonate moiety of **5** are shielded by the ring current of the neighboring aromatic

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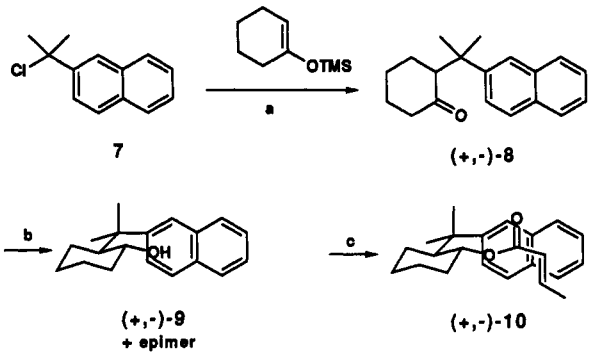
nucleus, the magnitude of the shielding depending strongly on the size (and shape) of this nucleus. Very interestingly an excellent correlation between the shielding of the protons of the crotonate part of esters **5** and the selectivities in their conjugate addition of certain nucleophiles has also been observed: *the greater the shielding, the higher the selectivity*, an almost complete stereocontrol having been achieved with the β-naphthyl derivative. Thus, high pressure-promoted addition of diphenylmethaneamine to **5** (Ar = H, Ph, β-naphthyl) in methanol led to the expected Michael adducts **6** with diastereomeric excesses (de) of 10%, 60%, and 99%, respectively.[1c] *It is worthy of note that the preceding NMR experiment constitutes a very simple test to probe the efficacy of a given chiral auxiliary in this series.*

Recently a semiempirical theoretical study of crotonates **5** has been performed by Giessner-Prettre and co-workers by resorting the SIBFA calculation method.[9] According to these calculations, where the stacked and the nonstacked conformations of **5** (Ar = Ph) are nearly isoenergetical, *the stacked conformation of* **5** (Ar = β-naphthyl) *was found to be the most stable by 3.1 kcal/mol.* Thus, it appears, on the basis of the previous observations, that a binding interaction arises in 8-arylmenthyl crotonates **5** (particularly marked in the case of the β-naphthyl derivative) between the electron-rich aromatic nucleus and the π-deficient crotonate fragment, engaged in a compact, stacked arrangement.[6] However, to be valid, such a model should fulfill two criteria: the rough parallelism of the neighboring π-systems[6] and an interplanar separation distance of these systems in the range of 3.4–4 Å,[6,10] two geometrical parameters whose determination requires the crystal structure analysis of the present molecules.

In view of the fact that "aromatic" crotonates **5** (Ar = Ph, β-naphthyl) are oils at room temperature, we have undertaken the preparation of a "*simplified*" equivalent, namely the crotonic acid ester of *trans*-2-[1-(2-naphthyl)-1-methylethyl]cyclohexanol **10** (the analogous structure of **5**, Ar = β-naphthyl, lacking only the methyl substituent on the cyclohexane ring).[11,12] For this purpose, requisite parent alcohol **9** was elaborated in its racemic form,[13] in a development of the procedure used by Whitesell for the preparation of the analogous phenyl derivative:[11a] addition of the tertiary chloride **7** to the trimethylsilyl enol ether of cyclohexanone in the presence of zinc chloride, followed by reduction of the resulting ketone **8** by means of Luche's reagent and separation of the mixture of epimeric alcohols by flash chromatography on silica gel (Scheme 3).

Crotonate **10** was found to be a nice crystalline compound, particularly well-suited for an X-ray diffraction analysis.[14,19] *This crystal structure shows that the two π-systems are close to each other and engaged in a roughly coplanar geometry*, as revealed by the distances from the

Scheme 3[a]



[a] Key: (a) 0.1 equiv of $ZnCl_2$, CH_2Cl_2, rt, 1 h, 94%; (b) $NaBH_4$, $CeCl_3$, MeOH, rt, 96% combined yield; (c) crotonic acid, DCC, cat. DMAP, CH_2Cl_2, rt, 14 h, 85%.

carbon centers of the crotonate moiety to the π-plane of the naphthalene (πp): C_8-πp, 3.41 Å; C_{10}-πp, 3.37 Å; C_{11}-πp, 4.03 Å; C_{12}-πp, 3.99 Å (Figure 1). On the other hand, viewing the molecule perpendicularly to the naphthalene plane shows that the W-shaped crotonate segment OCC=CC superimposes approximately with the five-carbon array of the underlying upper edge of the naphthalene, with a lateral offset between the carbon centers of 0.7–0.9 Å. Another remarkable feature of this structure is the *s-cis,syn* conformation of the crotonate chain. This is in agreement with a recent theoretical study which has established that the *s-cis,syn* conformation of methyl acrylate is more stable than the *s-trans,syn* conformer by 0.7 kcal/mol, in the vapor phase.[15]

As expected, the ^1H NMR spectrum of **10** indicates that the protons of the crotonate part are strongly shielded, a phenomenon which corroborates the close proximity of the two π-systems. Seeing that the magnitude of this shielding and the one observed with the crotonate of 8-(2-naphthyl)menthol **5** (Ar = β-naphthyl) (*vide supra*) are *in all points identical*, the parent alcohol **9** was suspected to be a powerful chiral auxiliary. This was actually confirmed by the high-pressure-mediated conjugate addition of diphenylmethaneamine to crotonate **10** (MeOH, 15 kbar):[1c] the Michael adduct **11** was obtained with a very high de (98%) (Scheme 2).

However, at first sight rather surprisingly, the configuration of the newly created stereogenic center in adduct **11** corresponds to the preferred approach of the amine from the sterically less congested π-face of the crotonate moiety of **10**,[16] *depicted in its s-trans,syn conformation* (as was observed in the addition of diphenylmethaneamine to crotonate **5**, Ar = β-naphthyl).[1c] This stereochemical finding appears to be in contradiction with the *s-cis,syn* conformation exhibited by starting crotonate **10** in the

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(16) The diastereomeric ratio and the sense of induction in adduct **11** have been determined by comparing its ^1H NMR spectrum with those of the analogous adducts in the 8-arylmenthol series.[1c]

solid state. Nevertheless, it should be emphasized that the preceding additions require imperatively to be performed in a *polar, protic solvent*, usually methanol (thus, these reactions completely failed when THF or dichloromethane were used as a solvent), a medium which stabilizes to a larger extent the *s-trans,syn* conformational isomer of enoates.[15]

It is clear, as far as the π-stacking interaction in crotonate **10** governs the geometry of the transition state of the present Michael addition, that the high level of the observed stereocontrol originates from the cofacial arrangement of the overlapped π-systems in this crotonate. In this respect, as pointed out in the space-filling diagram of Figure 1, the naphthalene nucleus plays the role of a "*stereoblocking group*" which definitively prevents the arrival of any reagent from the adjacent π-face of the stacked crotonate appendage. Seeing that the tremendous efficacy as chiral inducer of 8-(2-naphthyl)menthol **1** (Ar = β-naphthyl)[1c] is preserved in alcohol **9**, the latter can be considered as a "simplified substitute" of the former. Work is in progress in our laboratory to extend the scope of applications of this highly promising auxiliary in asymmetric synthesis.

Experimental Section

Melting points were recorded on a Kofler bench. IR spectra were recorded on a Perkin-Elmer 841 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Brüker AC 200 or Brüker AC 300 spectrometers in deuteriochloroform; the observed chemical shifts are given in ppm from tetramethylsilane.

2-(2-Naphthyl)-2-chloropropane (7). To 25 g of 2-(2-naphthyl)-2-hydroxypropane in dichloromethane (25 mL) at 0 °C was slowly added 125 mL of 12 N hydrochloric acid. After the mixture was stirred for 24 h at room temperature, the organic phase was diluted with CH_2Cl_2, washed with aqueous sodium hydrogenocarbonate (100 mL) and brine (100 mL), and dried over sodium sulfate. The organic filtrate was concentrated and the residue used immediately without any further purification (24.8 g, 94% yield): oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (s 6H), 7.2–7.6 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.4 (C), 132.7 (C), 132.5 (C), 128.3 (CH), 128.1 (CH), 127.4 (CH), 126.3 (2 CH), 124.6 (CH), 123.1 (CH), 69.7 (C), 34.1 (2 CH_3).

Racemic 2-[1-(Naphthyl)-1-methylethyl]cyclohexanone (8). To 27 g (0.15 mol) of 1-(trimethylsiloxy)-1-cyclohexene and 23 g (0.11 mol) of chloride **7** in 400 mL of anhydrous CH_2Cl_2 was added 22 mL of a 1 M solution of zinc chloride in ether (22 mmol). The mixture was stirred at room temperature for 30 min and poured into cold water. The aqueous layer was separated and extracted with three 100-mL portions of ether. The organic layers were combined, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude was chromatographed over silica gel (cyclohexane/ether (9:1)) to yield 27.6 g (94%) of pure ketone **8** (by HPLC): mp 61 °C (MeOH); IR (neat) 3045, 2946, 1710, 1449, 1122 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8–7.7 (m, 4H), 7.53 (dd, 1H, J = 8.7, 1.9 Hz), 7.4–7.2 (m, 2H), 2.84 (dd, 1H, J = 11.4, 4.4 Hz), 2.4–2.3 (m, 2H), 2.1–1.9 (m, 1H), 1.8–1.4 (m, 5H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0 (C=O), 147.2 (C), 133.3 (C), 131.7 (C), 128.0 (CH), 127.6 (CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 124.6 (CH), 124.3 (CH), 60.1 (CH), 44.2 (CH_2), 39.5 (C), 30.3 (CH_2), 28.5 (CH_2), 26.9 (CH_3), 26.0 (CH_2), 23.6 (CH_3); MS (EI, 70 eV) *m/e* 266 (M^+, 36), 250 (75), 208 (100), 207 (61), 105 (45).

Racemic *trans*-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexanol (9). Ketone **8** (2.2 g, 8.3 mmol) was allowed to complex with anhydrous cerium trichloride (2.05 g, 1 equiv) in 18 mL of absolute methanol at room temperature for 1 h. Sodium borohydride (314 mg, 1 equiv) was then added in small portions. The mixture was stirred for 2 h, treated with 10% hydrochloric acid, extracted twice with Et_2O, and dried over $MgSO_4$. The crude (3/2 mixture of *cis/trans* alcohols) was chromatographed over silica gel (cyclohexane/AcOEt (95:5)) to yield 800 mg of the *trans* isomer **9** (36% yield) and 1.2 g of the *cis* isomer (54% yield). Alcohol **9**: mp 71–72 °C (pentane); IR (neat) 3584, 3446, 3064, 2931, 1601, 1449 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84–7.77 (m, 4H), 7.61–7.56 (dd, 1H, J = 1.9, 8.7 Hz), 7.47–7.42 (m, 2H), 3.56 (ddd, 1H, J = 4.8, 8.7, 9.2 Hz), 1.94–1.83 (m, 2H), 1.76–1.55 (m, 3H), 1.55 (s, 3H), 1.38 (s, 3H), 1.26–1.18 (m, 3H), 1.12–1.04 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9 (C), 133.3 (C), 131.6 (C), 127.9 (2 CH), 127.3 (CH), 125.8 (CH), 125.4 (CH), 125.1 (CH), 123.1 (CH), 73.4 (CH), 54.0 (CH), 40.2 (CH_2), 36.7 (CH_2), 27.8 (CH_3), 26.9 (CH_2), 26.2 (CH_2), 25.1 (CH_3), 25.0 (CH_2). Anal. Calcd for $C_{19}H_{24}O$: C, 85.07; H, 8.95. Found: C, 84.99; H, 9.0. Cis isomer: mp 78 °C (pentane); IR (neat) 3456, 2936, 1636 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86–7.79 (m, 4H), 7.55 (dd, 1H, J = 8.8, 1.7 Hz), 7.49–7.43 (m, 2H), 3.87 (m, 1H), 1.87–1.05 (m, 10H), 1.52 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.4 (C), 133.2 (C), 131.6 (C), 128.0 (CH), 127.4 (CH), 127.2 (CH), 125.8 (CH), 125.3 (CH), 125.2 (CH), 124.3 (CH), 67.8 (CHOH), 52.1 (CH), 40.6 (CH_2), 35.1 (CH_2), 27.6 (CH_3), 26.9 (CH_2), 25.6 (CH_3), 21.4 (CH_2), 19.9 (CH_2).

Racemic *trans*-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl-(*E*)-2-butenoate (10). To a solution of 1.85 g (6.9 mmol) of alcohol **9**, 1.18 g (13.8 mmol) of crotonic acid, and 109 mg (0.9 mmol) of DMAP in CH_2Cl_2 (15 mL) at 0 °C was added dropwise 1.85 g (9 mmol) of DCC in 3 mL of CH_2Cl_2. After 14 h at room temperature, the excess DCC was consumed with methanol (0.5 mL). The dicyclohexylurea was filtered off and the filtrate washed successively with 0.5 N hydrochloric acid (50 mL), saturated aqueous hydrogenocarbonate (50 mL), and brine (50 mL), dried over $MgSO_4$, and concentrated. Chromatography of the crude product afforded 1.97 g (85%) of pure crotonate **10**: mp 87 °C (hexane); IR (neat) 3426, 2940, 1707, 1661, 1449 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75–7.63 (m, 3H), 7.55–7.42 (m, 2H), 7.38–7.25 (m, 2H), 6.06 (dq, 1H, J = 15.5, 6.9 Hz), 4.93 (dq, 1H, J = 15.5, 1.6 Hz), 4.8 (m, 1H), 2.15 (ddd, 1H, J = 11.2, 11.2, 3.5 Hz), 1.79 (m, 2H), 1.7–1.6 (m, 2H), 1.34 (s, 3H), 1.25–1.0 (m, 4H), 1.20 (s, 3H), 1.15 (dd, 3H, J = 6.9, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C=O), 150.2 (C), 144.6 (CH), 134.5 (C), 132.2 (C), 128.7 (CH), 128.0 (CH), 127.9 (CH), 126.6 (CH), 125.8 (CH), 125.7 (CH), 123.9 (CH), 123.4 (CH), 74.8 (CHOH), 51.3 (CH), 40.7 (C), 34.2 (CH_2), 29.3 (CH_3), 27.8 (CH_2), 26.9 (CH_2), 25.6 (CH_2), 24.7 (CH_3), 18.1 (CH_3). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.14; H, 8.33. Found: C, 82.04; H, 8.41.

X-ray crystal analysis: molecular weight 336.47; crystal obtained by slow evaporation of a solution of **10** from pentane/diethyl ether (1:1); orthorhombic system; space group *Pbca*; Z = 8; a = 8.169(3) Å, b = 23.082(9) Å, c = 20.649(8) Å; V = 3893(2) Å^3; d = 1.15 g·cm^{-3}; $F(000)$ = 1472; λ = (Cu Kα) = 1.5418 Å, μ = 5.2 cm^{-1} (absorption ignored). Data were collected on a CAD4 Enraft-Nonius diffractometer with graphite-monochromated Cu Kα radiation. From the 5996 reflections measured by the θ-2θ scan technique up to θ = 67°, 3357 were independent (R_{int} = 0.032) and 2320 were considered as observed with $I > 3\sigma(I)$, $\sigma(I)$ from counting statistics. The structure was solved by direct methods with the program SHELXS86[17] and refined by full-matrix least-squares minimizing $\sum w(F_o - |F_c|)^2$ with the program SHELX76.[18] All hydrogen atoms were located on difference Fourier maps. Their coordinates were refined, and they were assigned the anisotropic factor equivalent to that of the bonded atom plus 20%. Convergence was reached at R = 0.045, Rw = 0.070 (with $Rw = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o\}^{1/2}$ = $w = 1/(\sigma 2(F_o) + 0.0023F_o^2)$. No residual was higher than 0.16 eÅ^{-3} in the final difference map.[19]

(1*R,2*R**,3*S**)-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexyl 3-((diphenylmethyl)amino)butyrate (11).** A solution of 202 mg (0.6 mmol) of crotonate **10** and 220 mg (0.66 mmol) of diphenylmethanamine in MeOH (0.5 mL) was pressurized at 15 Kbar at 20 °C for 5 h. After depressurization, the solvent was

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(18) Scheldrick, G. SHELX76. Program for crystal structure determination; University of Cambridge: United Kingdom, 1976.

(19) The author has deposited atomic coordinates for **10** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

removed and the residue chromatographed over silica gel (cyclohexane/AcOEt/triethylamine 17:2:1) to yield 202 mg (65%) of aminobutyrate 11: oil; IR (neat) 3346, 3067, 3032, 2937, 2860, 1725, 1633, 1601 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ major isomer 7.8–7.6 (m, 2H), 7.5–7.0 (m, 5H), 4.99 (ddd, 1H, J = 10.4, 10.4, 4.2 Hz), 4.78 (s, 1H), 2.78 (m, 1H), 2.3–1.9 (m, 2H), 1.8–0.7 (m, 9H), 1.43 (s, 3H), 1.24 (s, 3H), 0.78 (d, 3H, J = 6.6 Hz); minor isomer 4.84 (s, 1H), 0.65 (d, 3H, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.3 (C=O), 149.3 (C), 144.3 (C), 133.3 (C), 131.4 (C), 128.3 (4 CH), 127.8 (2CH), 127.5 (2 CH), 127.2 (4 CH), 126.8 (2 CH), 125.8 (CH), 125.1 (2 CH), 122.5 (CH), 74.5 (CHOH), 63.6 (CH), 50.3 (CH), 47.0 (CH), 41.4 (CH2), 39.9 (CH_2), 33.3 (CH_2), 28.1 (CH_3), 26.9 (CH_2), 26.0 (CH_2), 24.7 (CH_2), 24.3 (CH_3), 19.9 (CH_3).