Enantioselective Synthesis of Juvenile Hormone III in Three Steps from Methyl Farnesoate

Gerard A. Crispino, K. Barry Sharpless*

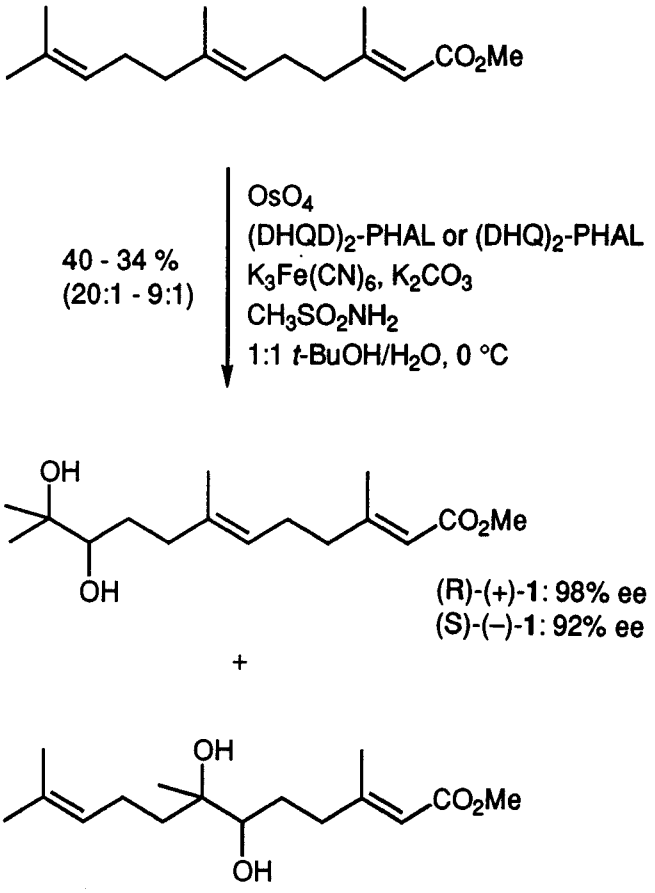
The Scripps Research Institute 10666 N. Torrey Pines Rd., La Jolla, California 92037, USA

Received 4 December 1992; revised 24 February 1993

The asymmetric dihydroxylation of methyl farnesoate resulted in regioselective dihydroxylation of the 10, 11 olefin to give the (10*S*)- and (10*R*)-(2*E*,6*E*)-10,11-dihydroxy-3,7,11-trimethyl-2,6-dodecadienoates in high ee. These diols were converted to juvenile hormone III and its enantiomer.

The osmium-catalyzed asymmetric dihydroxylation (AD) has recently been improved by the development of the phthalazine class of ligands and a new simplified procedure.[1] High enantiomeric excesses are now possible with four of the six classes of olefins, allowing the AD to enter the application phase. Of particular interest is the question of regioselectivity.[2,3] Recent work showed that AD of squalene resulted in preferential attack at the terminal, least congested olefinic site,[2] suggesting that similar selectivity might be observed for related polyenes such as methyl farnesoate. Regio- and stereoselective dihydroxylation of the terminal 10,11-olefinic bond would provide a simple stereospecific synthesis of juvenile hormone III (JH III) and its enantiomer.[4]

Dihydroxylation of methyl farnesoate with catalytic osmium tetroxide and potassium ferricyanide as cooxidant at 0 °C gave a 3:1 mixture of the 10, 11- and 6,7-diols along with tetrols and recovered starting material. The selectivity presumably arises from the different steric environments of the 10,11- and 6,7-olefins. Similar observations were made during the oxidation of methyl farnesoate with peracid[5] and dimethyldioxirane.[6] In light of these results, it was of interest to see how the phthalazine ligands would effect the ratio of 10,11- to 6,7-diol.



Scheme 1

Surprisingly, AD of methyl farnesoate (Scheme 1) with 5 mol % of 1,4-bis(dihydroquinidinephthalazine) [$(DHQD)_2$-PHAL][7] gave a 20:1 ratio of (*R*)-10,11- to 6,7-diol along with tetrol (+)-**3** and 15% recovered starting material. The increased selectivity favoring the 10,11-over the 6,7-olefinic bond may be due to increased steric liability caused by the presence of the ligand in the transition state. Under the same conditions, the ratio of 10,11- to 6,7-diol dropped to only 9:1 when 1,4-bis(dihydroquininephthalazine) [$(DHQ)_2$-PHAL] was used as the ligand. This drop in regioselectivity, like the drop in ee (92% compared to 98%), is a consequence of the non-enantiomeric relationship between the two ligands. Dihydroquinidine and dihydroquinine are actually diastereomers since they have opposite chirality at only four of the five stereogenic centers.

In both cases, appreciable amounts of tetrols (+)-**3** and (−)-**3** also formed (Figure 1). From ^{1}H NMR and GLC data these appear to be essentially a single diastereomer [traces of the other diastereomer were found when $(DHQ)_2$-PHAL was used]. Since the AD proceeds in high ee, it is reasonable to assume that each tetrol is nearly enantiomerically pure. Similar high multienantiofacial selectivity has also been observed in the 'exhaustive' AD

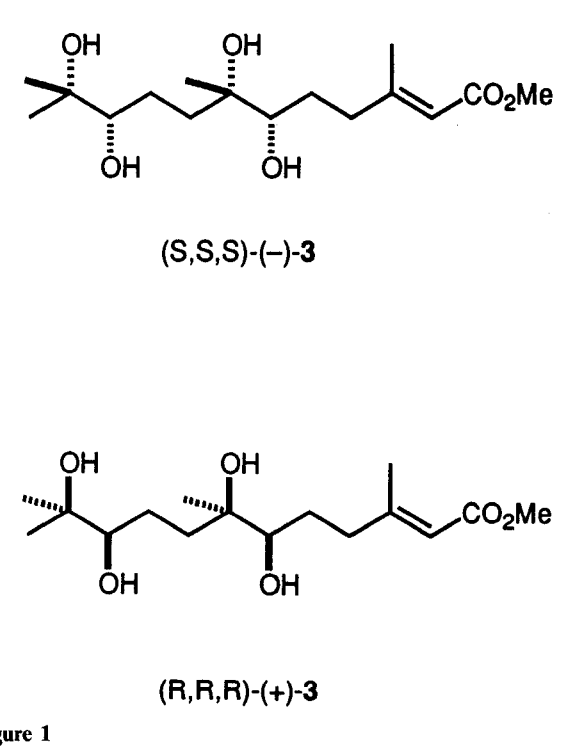
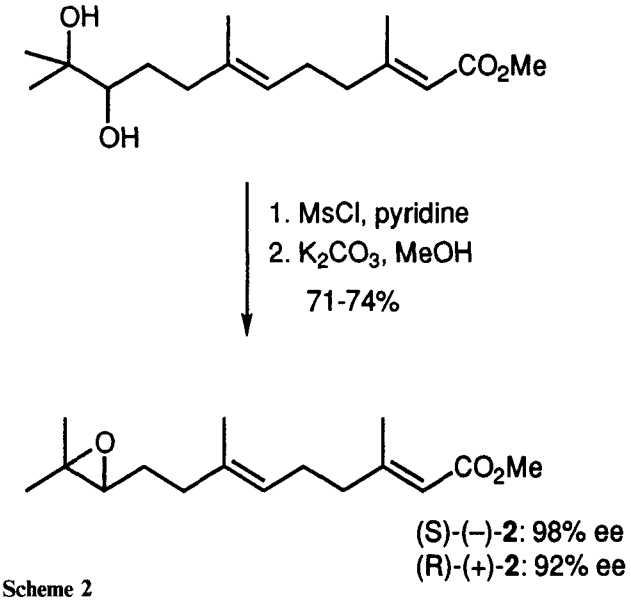


Figure 1

of squalene.[8] Therefore, $(DHQD)_2$-PHAL should give the (*R,R,R*)-tetrol, while $(DHQ)_2$-PHAL should give the (*S,S,S*)-tetrol. These tetrols were isolated as white crystals which could be recrystallized from benzene to give analytically pure compounds with equal and opposite optical rotations of $\pm 44.8°$.

The enantiomeric diols **1** were then converted into the enantiomeric epoxides **2** via the mesylates (mesyl chloride and pyridine), followed by ring closure with potassium carbonate in methanol (Scheme 2). Diol (−)-**1** gave the natural JHIII, (+)-**2**, in 92% ee and diol (+)-**1** gave the enantiomer of JHIII, (−)-**2**, in 98% ee. The overall ee's were determined by direct injection of the epoxides on a Chiralcel OF HPLC column with the UV detector set at 230 nm. These conditions gave a clean, baseline separation of the two enantiomers. (See the experimental section.)



Scheme 2

In summary, we have described a simple procedure for the preparation of JHIII and its enantiomer in high optical purity. This approach should be applicable to other juvenile hormones and their derivatives.

All reagents were purchased from Aldrich Chemical Co. and used without further purification. 1,4-Bis(dihydroquinine)phthalazine and 1,4-bis(dihydroquinidine)phthalazine were prepared as reported in ref. 1, they are now available from Aldrich Chemical Co. Solvents were obtained from EM Science. Melting points were determined with a Thomas-Hoover capillary melting point apparatus in open glass capillaries; the values are uncorrected. Analytical thin layer chromatography (TLC) was performed on Merck precoated glass plates (silica gel 60, F-254, 0.25 mm thick). Preparative flash column chromatography was performed using EM Reagents silica gel 60, 230–400 mesh. ^1H and ^{13}C NMR were recorded on a Bruker AMX 400 at 400 and 100 MHz, respectively. IR spectra were recorded on a Nicolet 510 FT-IR. Optical rotations were taken on a Rudolph Autopol III polarimeter. Elemental analyses were performed by Robertson Laboratories Inc., Madison, NJ. Compounds (+)-3 and (−)-3 gave C ± 0.29, H ± 0.23.

Methyl Farnesoate:
Methyl farnesoate was prepared in two steps from *trans,trans*-farnesol following the literature procedure;[9] the modified procedure of Prestwich[10] was used in the first step to prepare *trans, trans*-farnesal.

Osmylation of Methyl Farnesoate Without Ligand:
To a well stirred solution of $K_3Fe(CN)_6$ (1.98 g, 6 mmol), K_2CO_3 (0.84 g, 6 mmol), $MeSO_2NH_2$ (0.19 g, 2 mmol), and OsO_4 (2.0 mol %) in *t*-BuOH–water (1:1; 20 mL) at 0 °C was added freshly prepared methyl farnesoate (574 mg, 2.3 mmol). The mixture was stirred for 48 h, then $Na_2S_2O_5$ (3.0 g) was slowly added and the suspension warmed to room temperature. CH_2Cl_2 (20 mL) was added and the aqueous layer was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with aq 1 M KOH, dried ($MgSO_4$), and then concentrated. The ratio of 10,11- to 6,7-diol was determined to be 3:1 by GLC of the acetonides [J&W DB-23 (30 m × 0.32 mm I.D.), 180 °C]. The crude product was then flash chromatographed on silica (EtOAc–hexane, 1:2) to give recovered methyl farnesoate (0.107 g, 19%) followed by methyl (2*E*)-6,7-dihydroxy-3,7,11-trimethyl-2,10-dodecadienoate (0.062 g, 9.5%) as a clear, colorless oil.

IR (neat): ν = 3456 (OH), 2933, 1721 (C=O), 1650, 1438, 1227, 1152 cm^{-1}.

^1H NMR (CD_3OD): δ = 1.12 (s, 3H), 1.36–1.56 (m, 3H), 1.61 (s, 3H), 1.67 (s, 3H), 1.70–1.78 (m, 1H), 2.03–2.09 (m, 2H), 2.16 (s, 3H), 2.18–2.24 (m, 1H), 2.40–2.47 (m, 1H), 3.28 (d, J = 10.7 Hz, 1H), 3.65 (s, 3H), 5.09–5.13 (m, 1H), 5.73 (s, 1H).

^{13}C NMR (CD_3OD): δ = 15.14, 16.43, 19.82, 20.49, 23.33, 27.53, 36.24, 36.48, 48.67, 72.87, 75.20, 113.66, 123.31, 129.47, 159.41, 166.15.

HRMS (FAB+): Calc. for $C_{16}H_{28}O_4$ (M + Cs^+): 417.1042. Found: 417.1055.

Continued elution (EtOAc–hexane, 1:2) gave methyl (2*E*,6*E*)-10,11-dihydroxy-3,7,11-trimethyl-2,6-dodecadienoate, [(±)-**1**] (0.176 g, 27%) as a clear colorless oil. ^1H NMR and IR matched literature values.[4] Finally, elution with neat EtOAc gave an inseparable mixture of tetrols (0.158 g, 22%) as a clear, colorless oil which crystallized white. Spectral data of this mixture matched literature values.[6]

AD of Methyl Farnesoate Using $(DHQD)_2$-PHAL:
To a well stirred solution of $(DHQD)_2$-PHAL (40 mg, 5.0 mol%), $K_3Fe(CN)_6$ (0.99 g, 3 mmol), K_2CO_3 (0.42 g, 3 mmol), $MeSO_2NH_2$ (0.096 g, 1 mmol), and OsO_4 (1.0 mol %) in *t*-BuOH–water (1:1; 10 mL) at 0 °C was added freshly prepared methyl farnesoate (250 mg, 1.0 mmol). The mixture was stirred for 24 h, then $Na_2S_2O_5$ (1.5 g) was slowly added and the suspension warmed to room temperature. CH_2Cl_2 (10 mL) was added and the aqueous layer was further extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with aq 1 M KOH, dried ($MgSO_4$) and then concentrated. The ratio of 10,11- to 6,7-diol was determined to be 20:1 by GLC of the acetonides [J&W DB-23 (30 m × 0.32 mm I.D.), 180 °C] The crude product was then flash chromatographed on silica (EtOAc–hexane, 1:1) to give recovered methyl farnesoate (39 mg, 15%) and a mixture of the diols (114 mg, 39,5%), which were rechromatographed under the same conditions to give pure methyl (2*E*,6*E*,10*R*)-10,11-dihydroxy-3,7,11-trimethyl-2,6-dodecadienoate [(+)-**1**] (93 mg, 32%, 98% ee) as a viscous oil. $[\alpha]_D^{26}$ + 21.3° (c = 0.78, MeOH) {lit.[11] $[\alpha]_D$ + 17.8° (c = 1.8, MeOH)}; ^1H NMR and IR matched literature values.[4]

The ee was determined by preparing the cyclic carbonate (1–2 mg of 10,11-diol, 10 mg of DMAP, and 10 mg of triphosgene in 500 µL of dry CH_2Cl_2) and injecting on a Chiralcel OG HPLC column using 5.0% *i*-PrOH in hexane and a 1.0 mL/min flow rate; the UV detector was set to 230 nm. (The retention times of the (*S*)- and (*R*)-10,11-diols are 28.6 and 33.1 min, respectively.)

Further elution of the first column with neat EtOAc gave tetrol (+)-**3** (117 mg, 36.8%). The ^1H NMR showed one diastereomer with traces of impurity. One recrystallization from benzene gave white fluffy crystals, mp 97–98 °C. $[\alpha]_D^{25}$ + 44.8° (c = 0.42, MeOH).

IR (KBr): ν = 3367 (OH), 2971, 1711 (C=O), 1650, 1225, 1148, 1075, 949 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.08 (s, 3H), 1.14 (s, 3H), 1.19 (s, 3H), 1.42–1.73 (m, 6H), 2.15 (s, 3H), 2.17–2.23 (m, 1H), 2.39–2.46 (m, 1H), 2.71 (bs, 1H, OH), 3.15 (bs, 1H, OH), 3.31 (d, J = 10.2 Hz,

2H), 3.66 (s, 3H), 3.74 (bs, 1H, OH), 3.87 (bs, 1H, OH), 5.70 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 18.91, 20.55, 23.32, 24.93, 26.53, 29.04, 35.67, 37.81, 50.87, 73.19, 74.48, 77.06, 78.98, 115.44, 160.04, 167.26.

HRMS (FAB+): Calc. for $C_{16}H_{30}O_6$ (M + Cs^+): 451.1097. Found: 451.1090.

AD of Methyl Farnesoate Using $(DHQ)_2$-PHAL:
This reaction was performed exactly as above except that $(DHQ)_2$-PHAL (40 mg, 5.0 mol %) was used. Chromatography gave recovered methyl farnesoate (33 mg, 13.5%) and a mixture of the 10,11- and 6,7-diols (95 mg, 34%) which were rechromatographed under the same conditions to give pure methyl (2*E*,6*E*,10*S*)-10,11-dihydroxy-3,7,11-trimethyl-2,6-dodecadienoate [(−)-**1**] (78 mg, 28%, 92% ee) as a viscous oil. $[\alpha]_D^{25}$ −20.1° (*c* = 0.6, MeOH) {lit.[4] $[\alpha]_D^{24}$ −18.9° (*c* = 1.24, MeOH)}. ^{1}H NMR and IR matched literature values.[4] The ee was determined as described above for (+)-**1**.

Further elution of the first column gave tetrol (−)-**3** (89 mg, 29%). The ^{1}H NMR showed one diastereomer with traces of impurity. One recrystallization from benzene gave white fluffy crystals. The mp and spectral data matched those given for its enantiomer. $[\alpha]_D^{25}$ −44.8° (*c* = 0.32, MeOH).

HRMS (FAB+): Calc. for $C_{16}H_{30}O_6$ (M + Cs^+): 451.1097. Found: 451.1097

Methyl (2*E*,6*E*,10*S*)-(−)-10,11-Epoxy-3,7,11-trimethyl-2,6-dodecadienoate (−)-2:
To a solution of (*R*)-10,11-diol (+)-**1** (88 mg, 0.31 mmol) in dry CH_2Cl_2 (10 mL) was added dry pyridine (1.0 mL, 12.4 mmol). The solution was cooled to 0°C and mesyl chloride (250 µL, 3.2 mmol) was added. After 5 min the solution was warmed to r.t. and stirred for 4 h. Then, more CH_2Cl_2 (10 mL) was added and the combined solutions were washed with saturated aq $CuSO_4$ (2X), H_2O, and brine, then dried ($MgSO_4$). Removal of the solvent in vacuo gave an oil which was used directly in the next step. The mesylate was then dissolved in absolute MeOH (20 mL), K_2CO_3 (500 mg, 3.6 mmol) was added, and the suspension stirred vigorously for 0.5 h. The suspension was then filtered through Florisil and the residue washed with hexane. The solvents were removed in vacuo and the residue partitioned between hexane and H_2O. After separation of the layers, the aqueous layer was extracted with hexane and the combined organic phase dried ($MgSO_4$). Filtration and concentration in vacuo gave an oil which was chromatographed on flash silica with 10:1 hexane–EtOAc as eluent. The enantiomer of JHIII, (−)-**2**, (59 mg, 71%, 98% ee) was obtained as a clear, colorless oil. $[\alpha]_D^{26}$ −6.0° (*c* = 0.48, MeOH), {lit.[4] $[\alpha]_D^{23}$ −6.55° (*c* = 0.25, MeOH)}. ^{1}H NMR and IR matched literature values.[4] The ee was determined by direct injection on a Chiralcel OF HPLC column using 2.5% *i*-PrOH in hexane with a 1.0 mL/min flow rate. The UV detector was set to 230 nm. (The retention times of the *R* and *S* enantiomers of JHIII are 13.8 and 16.1 min, respectively.)

Methyl (2*E*,6*E*,10*R*)-(+)-10,11-Epoxy-3,7,11-trimethyl-2,6-dodecadienoate (+)-2; JHIII:
The natural juvenile hormone (+)-**2** was obtained in 74% yield from the (*S*)-10,11-diol (−)-**1** following the above procedure. $[\alpha]_D^{26}$ +6.4° (*c* = 0.46, MeOH) {lit.[4] $[\alpha]_D^{24}$ +6.71° (*c* = 0.57, MeOH)}. ^{1}H NMR and IR matched literature values.[4] Analysis on the Chiralcel OF column using the above conditions showed 92% ee.

We are grateful to Professor Glenn Prestwich and Mr. Kavish Bhatnagar (SUNY Stony Brook) for helpful discussions, and the National Institutes of Health (GM 28384) for financial support.

(1) Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
(2) Crispino, G.A.; Sharpless, K.B. *Tetrahedron Lett.* **1992**, *33*, 4273.
(3) Xu, D.; Crispino, G.A.; Sharpless, K.B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.
(4) For other stereospecific syntheses of JHIII see: Mori, K.; Mori, H. *Tetrahedron* **1987**, *43*, 4097, and references cited therein.
(5) Camps, F.; Messeguer, A.; Sánchez, F. *Tetrahedron* **1988**, *44*, 5161.
(6) Messeguer, A.; Sánchez-Baeza, F.; Casa, J.; Hammock, B.D. *Tetrahedron* **1991**, *47*, 1291.
(7) Due to the slow rate of reaction of methyl farnesoate and other polyenes, we usually add more osmium (1.0 mol %) and ligand (5.0 mol %) than is present in the commercially available AD-mixes (see ref. 1 for AD-mix composition).
(8) Crispino, G.A.; Ho, P.T.; Sharpless, K.B. *Science* **1993**, *259*, 64.
(9) Corey, E.J.; Gilman, N.W.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(10) Xiao, X-y.; Prestwich, G.D. *Synth. Commun.* **1990**, *20*, 3125.
(11) Imai, K.; Marumo, S.; Ohtaki, T. *Tetrahedron Lett.* **1976**, 1211.

Phase-Transfer Catalyzed Nucleophilic Addition of Arylalkanenitrile Carbanions to Substituted Propenylarenes[1]

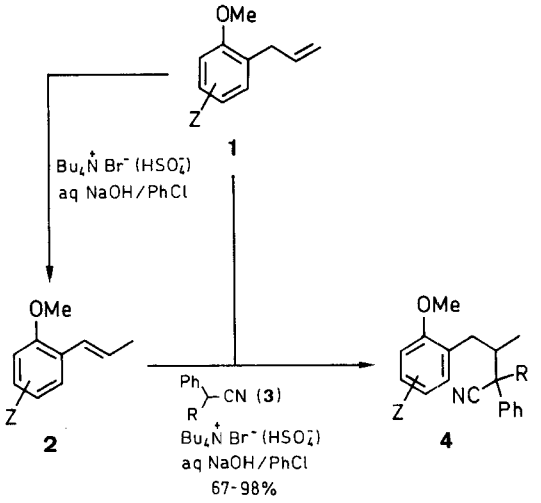
Wojciech Lasek, Mieczysław Mąkosza*
Institute of Organic Chemistry, Polish Academy of Sciences, PL-01-224 Warsaw, Kasprzaka 44/52, Poland
Received 29 January 1993
Dedicated to Professor E. V. Dehmlow on the occasion of his 60th birthday

Phenylacetonitrile and 2-phenylalkanenitriles react under phase transfer catalysis conditions with 2-propenylanisoles containing electron-withdrawing substituents (or their corresponding precursors, 2-allylanisoles) via the Michael addition pathway to give substituted 4-aryl-2-phenylbutyronitriles.

Phase-transfer catalysis is presently a general methodology for reactions of anionic species, particularly stabilized carbanions.[2] During the course of our studies on some mechanistic features of phase-transfer catalysis (PTC) we became interested in the base-catalyzed isomerization of allylarenes.[3] Although this process was already used for the isomerization of allylarenes,[4] in the present case we turned our attention to allylarenes, which could rearrange relatively easily; hence moderately electron-withdrawing substituents could be present in the aromatic ring. The simplest way of introducing an allyl group into the aromatic ring is by the Claisen rearrangement of allyl aryl ethers to *ortho*-allylphenols;[5] hence a series of the desired ethers were synthesised via *O*-allylation of substituted phenols. The ethers were thermally rearranged to *ortho*-allylphenols and the latter *O*-methylated to give the desired, substituted *ortho*-allylanisoles **1**.

Studies on the isomerization process catalyzed by the phenylacetonitrile carbanion generated in the PTC system showed that some propenylarenes – products of the isomerization – add subsequently the carbanion to produce 4-aryl-3-methyl-2-phenylbutyronitriles. On the other hand, the isomerization catalyzed by extracted OH^- anions proceeds without complication, giving the corresponding propenylanisoles, quantitatively.[3] On the basis of NMR spectra and GC analysis it was shown that all *o*-propenylanisoles are formed as the single *trans*-isomers. The ^1H NMR data of *o*-propenylanisoles **2a–e**, which were isolated[3] are given in Table 1 along with *o*-allylanisoles **1a–e**.

Since there are only a few examples of reactions, in which propenylarenes or unactivated alkenes act as Michael-type acceptors towards stabilized carbanions,[6] this process was studied extensively and was found to be general. Thus, not only phenylacetonitrile **(3a)** but also 2-phenylalkanenitriles **3b,c**, add to substituted *o*-propenylanisoles, giving the corresponding substituted 4-arylbutyronitriles **4** (Scheme). Since the educts in the addition process, substituted *o*-propenylanisoles **2**, are formed via the base-catalyzed isomerization of the *o*-allylanisoles **1** under essentially the same conditions, in the preparative experiments the former were used as the starting materials without affecting yields of the adducts. For the success of the reaction it is imperative to work under a strictly deoxygenated atmosphere, otherwise the tertiary nitrile carbanions are oxidized to the corresponding ketones.[7]



1, 2	Z	3	R
a	4-Br	**a**	H
b	3,4,6-Cl_3	**b**	Me
c	4,6-Br_2	**c**	Et
d	4-CN		
e	4-Cl,5,6-(CH=CH)$_2$		

4	Z	R	4	Z	R
ba	3,4,6-Cl_3	H	**db**	4-CN	Me
ca	4,6-Br_2	H	**eb**	4-Cl,5,6-(CH=CH)$_2$	Me
da	4-CN	H	**cc**	4,6-Br_2	Et
ea	4-Cl,5,6-(CH=CH)$_2$	H	**dc**	4-CN	Et
ab	4-Br	Me			

Scheme

In all the adducts **4** prepared, there are two chiral carbon atoms, hence they can be formed as two diastereoisomers. In the reaction with phenylacetonitrile, configuration of one stereogenic center can be changed via base-catalyzed epimerization; stereochemical results of the addition of 2-phenylalkanenitriles are kinetically controlled. As shown in Table 2, usually the isomeric products were formed in a ratio of about 1:1 and were not separated. The ratio of diastereoisomeric products was estimated on the basis of NMR spectra.

^1H NMR spectra were recorded on a Gemini Varian 200 MHz spectrometer with TMS as internal standard. Accurate mass measurements were done on Intectra AMD-604 mass spectrometer, using