The *Michael*-Type Addition Reaction: A Stereocontrolled Construction of a New Quaternary Chiral Center at C(2) of 2-(4-Hydroxybenzyl)cyclohexanone Derivatives

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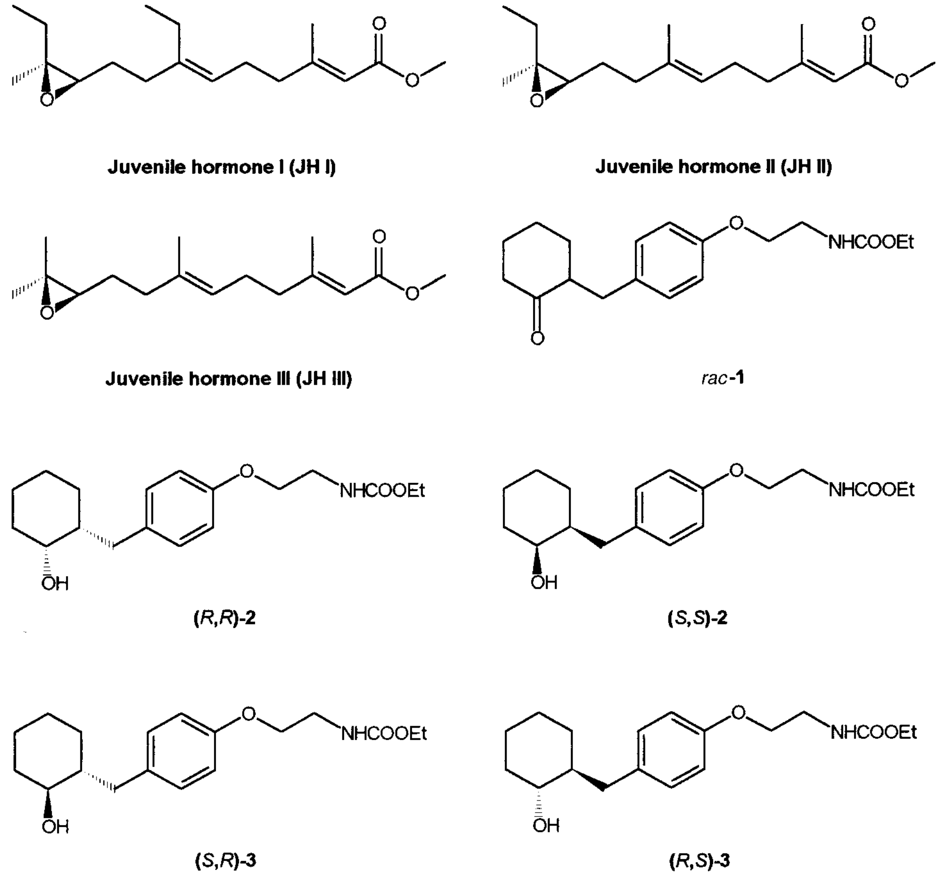
The *Michael*-type addition reaction was used as a convenient method for the stereocontrolled construction of a new quaternary C-center at position 2 of 2-substituted cyclohexanones (*Scheme*) with the aim to study the effect of an additional substituent at C(2) in a series of biologically active compounds bearing generally a 2-substituted cyclohexanone moiety. Thus, a new series of compounds consisting of a racemate (*RS*)-**12** and its enantiomers (*S*)- and (*R*)-**12** (ee $\geq$96% for both enantiomers) was obtained. The *Michael* adduct derivatives (*S*)-, (*R*)-, and (*RS*)-**12** were subjected to a biological screening using several non-related insect species.

Introduction. – The *Michael*-type addition reaction of chiral imines, obtained from racemic 2-substituted cycloalkanones and the enantiomerically pure (1-phenylethyl)-amine, to electrophilic alkenes under neutral conditions is a convenient method for the synthesis of enantiomerically pure 2,2-disubstituted cycloalkanones [1][2] and one of the most efficient procedures to construct a quaternary C-center under stereocontrol. Several such highly regioselective addition reactions displaying a remarkable control of absolute configuration of the adducts have been described [1–4]. Alkylation was shown to take place preferentially at the less hindered π-face of the more substituted secondary enamine [4]. A tautomeric equilibrium of the secondary enamine with the imine form is essential for high stereocontrol of the *Michael*-type addition. A tautomeric equilibrium is shifted in favor of the imine form; however, the secondary enamine form was suggested to be the reactive form for addition to electrophilic alkenes, as suggested by recent findings [4] during the synthesis of biologically active 2,2-disubstituted cycloalkanones.

Within the scope of our research on design and development of biologically active compounds, we studied a new series of potential insect juvenile hormone analogs (JHAs, juvenoids), *i.e.*, synthetic compounds that mimic natural insect juvenile hormones (JHs), *e.g.*, JH I, II, and III (*Fig.*). From the ecological point of view, in contrast to classical insecticides, these juvenoids represent a particularly attractive class of environmentally safe, biorational pesticides. A few years ago, a modified synthesis of a series of carbamate JHAs was published [5] which displayed excellent biological activities on a broad spectrum of insect pests. Thus, racemic cyclohexanone JHA *rac*-**1**



Juvenile hormone I (JH I)

Juvenile hormone II (JH II)

Juvenile hormone III (JH III)

rac-**1**

(*R*,*R*)-2

(*S*,*S*)-2

(*S*,*R*)-3

(*R*,*S*)-3

Figure. *Juvenile hormones and selected JHAs*

Table 1. *Biological Activity of JH I–III and of Several Reference JHAs on Yellow Mealworm* (*Tenebrio molitor*)

	Biological activity (*ID*$_{50}$ [µg/specimen])		Biological activity (*ID*$_{50}$ [µg/specimen])
JH I	$44.0 \cdot 10^{-6}$	JH III	inactive
JH II	$2000.0 \cdot 10^{-6}$	*rac*-**1**	$1.2 \cdot 10^{-6}$
(*S*,*S*)-**2**	$3.1 \cdot 10^{-6}$	(*S*,*R*)-**3**	$5.2 \cdot 10^{-6}$
(*R*,*R*)-**2**	$68.0 \cdot 10^{-6}$	(*R*,*S*)-**3**	$720.0 \cdot 10^{-6}$
rac-**2**	$53.0 \cdot 10^{-6}$	*rac*-**3**	$120.0 \cdot 10^{-6}$

(*Fig.*). exhibited an activity increase on the yellow mealworm (*Tenebrio molitor*) by more than one order of magnitude in comparison with the standard JH I, and by even higher orders of magnitude in comparison with JH II and III [5][6] (*cf. Table 1*).

Moreover, it was established that considerable differences in biological activity were observed with the stereoisomers of juvenoids, reflecting that a chiral receptor is involved in the insect recognition system [7]. For example, eutomers of the cyclohexanol-derived carbamate JHAs **2** and **3**, related to the cyclohexanone-derived carbamate JHA *rac*-**1**, proved to be more active than the corresponding distomers by one to two orders of magnitude (*Table 1*). Thus, it was of the greatest importance to compare the biological activities of the two enantiomers of ketone *rac*-**1**. However, such an endeavor appeared *a priori* unrealistic, considering the facile racemization of the substrate under both abiotic and biotic conditions. Therefore, we decided to stereoselectively synthesize, the non-epimerizable enantiomers of analogs of *rac*-**1** bearing an additional substituent at C(2) of the cyclohexanone moiety, by means of the above mentioned *Michael*-type addition of dural imines.

Results and Discussion. – The starting materials for the synthesis of the chiral imines (*R*)- and (*S*)-**7** and (*R*)- and (*S*)-**8** needed for the asymmetric *Michael* additions were the known [7] [8] racemic 2-[4-(methoxymethoxy)benzyl]cyclohexanone (**4**) and 2-(4-methoxybenzyl)cyclohexanone (**5**) which were converted into the imines in quantitative yield by condensation with the commercially available (*R*)-(1-phenylethyl)amine ((*R*)-**6**; 97% ee) or (*S*)-(1-phenylethyl)amine ((*S*)-**6**; 97% ee) (*Scheme*). The reaction was easily monitored by the intensity ratio of the characteristic IR bands at 1657 (C=N) and 1706 cm^{-1} (C=O).

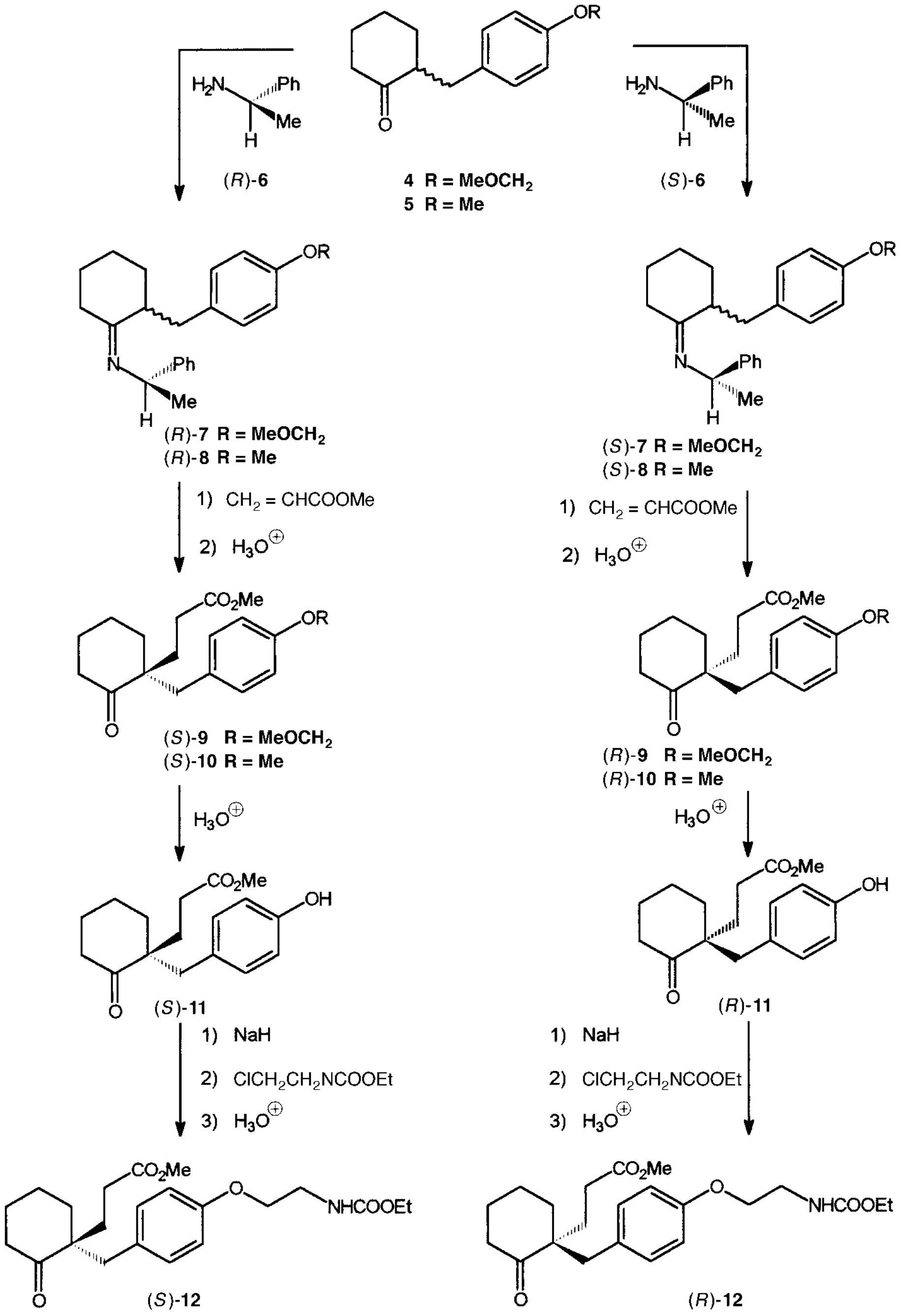
Our original objective [1–4] was to prepare asymmetric *Michael* adducts by reaction of the chiral imines **7** and **8** with phenyl vinyl sulfone ($PhSO_2CH{=}CH_2$) and next to reduce the sulfonyl appendage in the adducts into an ethyl group. However, even under forced conditions (toluene, 90°, 40 h), the *Michael* addition did not take place. In contrast, addition of the imines (*R*)- and (*S*)-**7** and (*R*)- and (*S*)-**8** to the more reactive methyl acrylate proceeded smoothly, furnishing after hydrolytic workup the expected adducts (*S*)- and (*R*)-**9** and (*S*)- and (*R*)-**10**, respectively, in good yield and excellent enantiomer excess (ee $\geq$96%; *Scheme*). To determine the latter, the ^{1}H-NMR spectrum of each enantiomer was recorded in the chiral solvating agent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (ee $\geq$99%) [9]. The reaction mechanism of the asymmetric *Michael*-type addition suggests an ee $\geq$97% (*i.e.*, the ee of the starting enantiomers (*R*)- and (*S*)-**6**); however, the possibly present minor components are not detectable by ^{1}H-NMR if they do not exceed 4%; thus the ee of all enantiomers **7** and **8** is $\geq$96%.

Routine reactions were then used to convert the chiral *Michael* adducts **9** and **10** into the target chiral JHAs (*S*)- and (*R*)-**12**. Removal of the methoxymethoxy or methoxy protecting group yielded the phenol derivatives (*S*)-**11** from (*S*)-**9** or (*S*)-**10** and (*R*)-**11** from (*R*)-**9** or (*R*)-**10**. Subsequently, the sodium salt of (*S*)- or (*R*)-**11** was reacted with ethyl (2-chloroethyl)carbamate to give (*S*)- and (*R*)-**12**, respectively.

In the racemic series, the cyclohexanones **4** or **5** were treated with racemic 1-phenylethylamine ((*RS*)-**6**), yielding the imines (*RS*)-**7** and (*RS*)-**8**, respectively, which were submitted to the *Michael* addition (→(*RS*)-**9** and (*RS*)-**10**, resp.). Subsequent deprotection (→(*RS*)-**11**) followed by reaction with ethyl (2-chloroethyl)carbamate afforded the racemic JHA (*RS*)-**12**.

Even if low or no biological activity of the target compounds (*S*)-, (*R*)-, and (*RS*)-**12** was expected, their juvenile hormone activity was tested on freshly ecdysed pupae of yellow mealworm (*Tenebrio molitor*) and on the last instar larvae of the Indian cotton stainer (*Dysdercus cingulatus*) and of the migratory locust (*Locusta migratoria migratorioides*). In topical assays, the ID_{50} value, which represent the dose causing 50%

Scheme. Michael *Addition of Methyl Acrylate and a Synthesis of the JHAs*



of morphological change in the insect development, *i.e.*, half-pupal adultoid, was assessed for (*S*)-, (*R*)-, and (*RS*)-**12** and compared with that of the natural juvenile hormones I and II (*Table 2*). The ID_{50} values are relatively high for (*S*)-, (*R*)-, and (*RS*)-**12** when tested on *T. molitor* and when compared with those for JH I and JH II, the racemic JHA (*RS*)-**12** being the least active and the enantiomers (*S*)- and (*R*)-**12** being slightly more active. The finding might indicate the existence of an antagonistic competition between the enantiomers (*S*)- and (*R*)-**12**, provided that they are mixed in the form of a racemate (*RS*)-**12**. In such a case, the simultaneous presence of both enantiomers (*S*)- and (*R*)-**12** in a mixture (*e.g.*, (*RS*)-**12**, racemic mixture) would reduce the resulting biological activity. However, the differences in the ID_{50} values are too small to support this hypothesis affirmatively. Moreover, at present it is impossible to indicate which enantiomer (*S*)- or (*R*)-**12** is responsible for the obtained results. In future studies, attention will be given to a possible inhibitory effect of one of the enantiomers, resulting in a decrease of biological activity of the racemic compound ((*RS*)-**12**).

Table 2. *Juvenile Hormone Activity* (ID_{50}) *of* (S)-, (R)-, *and* (RS)-**12** *in Topical Assays*

	Juvenile hormone activity (ID_{50} [µg/specimen])		
	Tenebrio molitor	*Dysdercus cingulatus*	*Locusta migratoria migratorioides*
JH I	0.000044	–	–
JH II	0.002	0.1	–
(*S*)-**12**	0.095	toxic	inactive
(*R*)-**12**	0.05	toxic	inactive
(*RS*)-**12**	0.14	toxic	inactive

The JHAs (*S*)-, (*R*)-, and (*RS*)-**12** were not active on *L. migratoria migratorioides*, and they displayed toxicity on *D. cingulatus* (*Table 2*). However, only a very low toxicity of the racemic (*RS*)-**12** was found when tested on virginoparae of the pea aphid (*Acyrthosiphon pisum*): the very high dose of 0.5 µg/individual of (*RS*)-**12** caused only 11.5% of mortality. For illustration, the toxicity of conventional insecticides, *e.g.*, of thiophosphates [10] for the peach aphid (*Myzus persicae*), is at least 4 orders of magnitude higher than that found with (*S*)-, (*R*)-, and (*RS*)-**12** on *A. pisum*.

No lethal toxic effect of (*S*)-, (*R*)-, and (*RS*)-**12** was observed in tests with females of the German cockroach (*Blattella germanica*) after 24 h following the application of high doses (50 or 100 µg per individual, which correspond to the doses of 1000 or 2000 µg/g) of the tested compounds. A gonadotropic activity of (*S*)-, (*R*)-, and (*RS*)-**12** was tested on adult cockroach females of *Blaberus craniifer*. An acetone solution of (*S*)-, (*R*)-, and (*RS*)-**12** was applied topically at imaginal molt (day 0; 100 µg per insect, *i.e.*, 30 µg/g). Activity was estimated at day 4 (after 96 h) on ovarian growth (the volume of basal oocyte and the total protein ovarian content) by comparison with the insect individuals treated with acetone alone (reference experiment). All three compounds showed a weak ovarian stimulation. The oocyte-volume values obtained for (*S*)-, (*R*)-, and (*RS*)-**12** in acetone with respect to the value obtained for the solvent acetone alone (reference value = 1) were 1.33, 1.42, and 1.15, respectively, indicating a higher gonadotropic effect found with both enantiomers (*S*)- and (*R*)-**12**. For ovarian protein content, the corresponding values were 1.45 ((*S*)-**12**), 1.21 ((*R*)-**12**), and 1.27

((*RS*)-**12**), respectively. It should be pointed out that the juvenile hormone III (see *Fig.*) displays a gonadotropic and vitellogenic activity on cockroaches [11][12]. This finding indicates that the design of a JHA displaying a satisfactory biological activity on these insects has never been an easy task.

Low juvenilizing activity of JH I and JH II was demonstrated in an assay on *Tenebrio molitor*, a holometabolous insect, but assays on two other paurometabolous species (*Locusta migratoria migratorioides* and *Blaberus craniifer*) for juvenilizing activity of JH III do not allow to conclude such a property only with the quantitative approach.

This project was supported by the *Ministry of Education of the Czech Republic* (COST projects D2.10 and D12.10) and by the *Grant Agency of the Czech Republic* (project No. GA CR 203/96/1617). *Z.W.* thanks the Université Paris-Sud for the financial support to cover his short-term visit to the Faculté de Pharmacie at Châtenay-Malabry (May 1996), and Mrs. *Martina Wimmerová* for her skillful assistance.

Experimental Part

General. Column chromatography (CC): silical gel (*Herrmann*, Köln-Ehrenfeld, FRG). TLC: precoated silica gel plates. HPLC: for purity checking; *TSP* (*Thermoseparation Products*) instrument, operated by a *Pentium* PC, using an OS-2 WARP/PC-1000 software; *ConstaMetric-4100-Bio* pump, *SpectroMonitor 5000 UV DAD*; column (250 × 4 (i.d.) mm) filled with a *Sepharon SGX Si C-18* (5 μm) reversed phase; (MeOH/H_2O 4 : 1) as mobile phase, flow rate 0.5 ml · min^{-1}. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter. IR Spectra: *Bruker-IFS-88* instrument (Czech Republic) or *Perkin-Elmer-841* spectrophotometer (France); $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian-Unity-500* spectrometer (FT model; ^{1}H at 499.8 and ^{13}C at 125.7 MHz) and *Varian-Unity-200* spectrometer (FT mode; ^{1}H at 200.1 MHz) (Czech Republic), or *Bruker-200* spectrometer (FT mode, ^{1}H at 200.13 MHz; France), in $CDCl_3$; δ in ppm, rel. to internal $SiMe_4$ ($\delta = 0.0$ for ^{1}H and 77.0 for ^{13}C), *J* in Hz.

*N-{(2*RS*)-2-{[4-(Methoxymethoxy)phenyl]methyl}cyclohexylidene}-α-methylbenzenemethanamines* **7** *and N-{(2*RS*)-2-[(4-methoxyphenyl)methyl]cyclohexylidene}-α-methylbenzenemethanamines* **8**. In a typical procedure, the racemic ketone **4** or **5** (24.2 mmol) and α-methylbenzenemethanamine (*R*)-, (*S*)-, or (*RS*)-**6** (29 mmol, *i.e.*, 20% molar excess) were dissolved in a minimum quantity of toluene (5 ml). The mixture was heated under N_2 and under azeotropic conditions for 25 – 30 h (IR monitoring). Then toluene and the excess of amine **6** were evaporated, and the residue was stored in a freezer at – 18°: 93 – 97% of **7** or **8**. IR (neat, **7** or **8**): 3083*w*, 3060*w*, 3028*m*, 2994*w*, 2964*m*, 2928*s*, 2857*m*, 2834*m*, 1657*m*, 1611*m*, 1604*w*, 1583*w*, 1512*s*, 1492*m*, 1463*m*, 1448*m*, 1367*w*, 1300*m*, 1246*s*, 1177*m*, 1111*w*, 1037*m*, 1010*w*, 831*m*, 761*m*, 700*s*, 679*m*. ^{1}-NMR ($CDCl_3$, 200.1 MHz; **7**): 1.15 – 1.90 (*m*, 6 H); 1.39 (*d*, *J* = 4.9, 3 H); 2.42 – 2.70 (*m*, 2 H); 2.52 (*d*, *J* = 13.9, 1 H); 2.58 (*d*, *J* = 13.9, 1 H); 3.08 – 3.25 (*m*, 1 H); 3.48 (*s*, 3 H); 4.72 (*q*, *J* = 4.9, 1 H); 5.13 (*s*, 2 H); 6.78 (*m*, 2 H); 7.10 (*m*, 2 H); 7.11 (*m*, 2 H); 7.18 (*m*, 2 H); 7.31 (*m*, 2 H). ^{1}H-NMR ($CDCl_3$, 200.1 MHz; **8**): 1.10 – 1.70 (*m*, 6 H); 1.38 (*d*, *J* = 4.9, 3 H); 2.42 – 2.70 (*m*, 2 H); 2.52 (*d*, *J* = 13.9, 1 H); 2.58 (*d*, *J* = 13.9, 1 H); 3.08 – 3.25 (*m*, 1 H); 3.78 (*s*, 3 H); 4.72 (*q*, *J* = 4.9, 1 H); 6.78 (*m*, 2 H); 7.10 (*m*, 2 H); 7.11 (*m*, 2 H); 7.18 (*m*, 2 H); 7.31 (*m*, 2 H).

*Methyl (*S*)-, (*R*)-, and (*RS*)-1-{[4-(Methoxymethoxy)phenyl]methyl}-2-oxocyclohexanepropanoate* ((*S*)-, (*R*)-, and (*RS*)-**9**, resp.) *and Methyl (*S*)-, (*R*)-, and (*RS*)-[(4-Methoxyphenyl)methyl]-2-oxocyclohexanepropanoate* ((*S*)-, (*R*)-, and (*RS*)-**10**, resp.). Michael-*Type Addition:* In a typical procedure, a soln. of **7** or **8** (0.714 mmol) in methyl acrylate (4 ml, important molar excess) was heated to 40 – 50° under N_2 and under vigorous stirring. After completion of the reaction (6 days) the excess of methyl acrylate was evaporated, the residue taken up in THF/MeOH 1 : 1 (4 ml), 10% aq. AcOH soln. (2 ml) added, and the mixture stirred overnight at r.t. The solvent was then evaporated, the residue extracted with CH_2Cl_2, the org. phase dried ($MgSO_4$) and evaporated, and the residue purified by CC: 70 – 80% of **9** or **10**, resp. (*S*)-**9**: $[\alpha]_D^{20} = -6.1$ (c = 0.45, $CHCl_3$). (*S*)-**10**: $[\alpha]_D^{20} = -6.5$ (c = 0.4, $CHCl_3$). (*R*)-**9**: $[\alpha]_D^{20} = +6.7$ (c = 0.5, $CHCl_3$). (*R*)-**10**: $[\alpha]_D^{20} = +6.5$ (c = 0.4, $CHCl_3$). IR ($CHCl_3$, **9** or **10**): 1740*s*, 1704*s*, 1258*m*. ^{1}H-NMR ($CDCl_3$, 200.1 MHz; **9**): 1.56 – 1.92 (*m*, 6 H); 1.78 (*ddd*, *J* = 5.4, 11.2, 14.1, 1 H); 1.93 (*ddd*, *J* = 5.1, 11.2, 14.1, 1 H); 2.11 (*ddd*, *J* = 5.1, 11.2, 15.9, 1 H); 2.40 (*ddd*, *J* = 5.4, 11.2, 15.9, 1 H); 2.43 – 2.45 (*m*, 2 H); 2.78 (*d*, *J* = 13.9, 1 H); 2.85 (*d*, *J* = 13.9, 1 H); 3.47 (*s*, 3 H); 3.66 (*s*, 3 H); 5.15 (*s*, 2 H); 6.92 (*m*, 2 H); 7.01 (*m*, 2 H). ^{1}H-NMR ($CDCl_3$, 200.1 MHz; **10**): 1.56 – 1.92 (*m*, 6 H); 1.78 (*ddd*, *J* = 5.4, 11.2, 14.1, 1 H); 1.93 (*ddd*, *J* = 5.1, 11.2, 14.1, 1 H); 2.11 (*ddd*, *J* = 5.1, 11.2, 15.9, 1 H); 2.40 (*ddd*, *J* = 5.4, 11.2, 15.9, 1 H); 2.43 – 2.45 (*m*, 2 H); 2.78 (*d*, *J* = 13.9, 1 H); 2.85 (*d*, *J* = 13.9, 1 H); 3.66

(*s*, 3 H); 3.78 (*s*, 3 H); 6.80 (*m*, 2 H); 7.01 (*m*, 2 H). MS (**9**): 334 (20, M^+), 107 (100). MS (**10**): 304 (25, M^+), 107 (100). Anal. calc. for $C_{19}H_{26}O_5$ (334.41; **9**): C 68.23, H 7.84; found ((*S*)-**9**): C 68.80, H 7.51; found ((*R*)-**9**): C 68.91, H 7.63; found ((*RS*)-**9**): C 68.57, H 7.62. Anal. calc. for $C_{18}H_{24}O_4$ (304.38; **10**): C 71.02, H 7.95; found ((*S*)-**10**): C 70.69, H 7.79; found ((*R*)-**10**): C 70.81, H 8.10; found ((*RS*)-**10**): C 70.79, H 7.83.

Methyl (S)-, (R)-, *and* (RS)*-1-[(4-Hydroxyphenyl)methyl]-2-oxocyclohexanepropanoate* ((*S*)-, (*R*)-, and (*RS*)-**11**, resp.). a) *Removal of the Methoxymethyl (MOM) Protecting group.* In a typical procedure, a soln. of **9** (1.91 mmol) in benzene/EtOH 1:1 (20 ml) was heated to 40° for 8 h. Then the solvent was evaporated and the residue chromatographed (silica gel): 90–95% of **11**. M.p. 96–97°. IR ($CHCl_3$): 3605*w*, 1740*s*, 1706*s*, 1258*m*. ^{1}H-NMR ($CDCl_3$, 200.1 MHz): 1.57–1.80 (*m*, 6 H); 1.81 (*ddd*, $J = 5.3$, 11.5, 14.1, 1 H); 1.90 (*ddd*, $J = 5.1$, 11.1, 14.1, 1 H); 2.13 (*ddd*, $J = 5.1$, 11.5, 16.2, 1 H); 2.40 (*ddd*, $J = 5.3$, 11.1, 16.2, 1 H); 2.40–2.49 (*m*, 2 H); 2.81 (*m*, 2 H); 3.66 (*s*, 3 H); 5.83 (br. *s*, 1 H); 6.74 (*m*, 2 H); 6.97 (*m*, 2 H). MS: 204 (30, M^+), 175 (17), 107 (100), 94 (11). Anal. calc. for $C_{13}H_{16}O_2$ (204.26): C 76.44, H 7.90; found ((*S*)-**11**): C 76.90, H 7.99; found ((*R*)-**11**): C 76.79, H 7.89; found ((*RS*)-**11**): C 76.86, H 7.99.

b) *Removal of the Methyl Protecting Group.* In a typical procedure, 48% hydrobromic acid (1.2 g) was added to a soln. of **10** (2.34 mmol) in Ac_2O (1.2 g) at r.t. The resulting mixture was heated to boiling for 4 h. After cooling to 0°, H_2O (8 ml) was added dropwise, the mixture neutralized by a portionwise addition of $CaCO_3$ (9.3 g), the precipitate filtered off and washed several times with Et_2O, the resulting filtrate dried (Na_2SO_4) and evaporated, and the residue purified by CC (silica gel): 55–65% of **11**. Spectra: corresponding to those mentioned above for the same products.

Methyl (S)-, (R)-, *and* (RS)*-1-{{4-{2-[(Ethoxycarbonyl)amino]ethyl}phenyl}methyl}-2-oxocyclohexanepropanoate* ((*S*)-, (*R*)-, and (*RS*)-**12**, resp.). In a typical procedure, a 50% dispersion of NaH in mineral oil (6.03 mmol of NaH) was added to a soln. of **11** (6.03 mmol) in DMF (35 ml) at r.t. under N_2. The mixture was stirred for 1 h. A soln. of ethyl (2-chloroethyl)carbamate (7.9 mmol) in DMF (5 ml) was added quickly under stirring, and the resulting mixture was heated up to 110° for 6–7 h. The mixture was then allowed to stand overnight at r.t. and then poured onto ice/10% aq. HCl soln. The org. layer was extracted with Et_2O/light petroleum ether 1:1 (4 ×, 100 ml overall). Evaporation and CC of the residue afforded 65–72% of **12**. (*S*)-**12**: $[\alpha]_D^{20} = -7.5$ ($c = 0.45$, $CHCl_3$). (*R*)-**12**: $[\alpha]_D^{20} = 7.8$ ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$): 3454*m*, 3390*w*, 1732*s*, 1716*s*, 1704*s*, 1612*m*, 1511*s*, 1438*s*, 1248*s*, 1179*s*, 1069*m*, 1047*m*. ^{1}H-NMR ($CDCl_3$, 200.1 and 499.8 MHz): 1.25 (*t*, $J = 7.1$, 3 H); 1.57–1.85 (*m*, 6 H); 1.77 (*ddd*, $J = 5.4$, 11.4, 14.2, 1 H); 1.93 (*ddd*, $J = 5.1$, 11.2, 14.2, 1 H); 2.11 (*ddd*, $J = 5.2$, 11.4, 16.4, 1 H); 2.39 (*ddd*, $J = 5.4$, 11.2, 16.4, 1 H); 2.42–2.45 (*m*, 6 H); 2.77 (*d*, $J = 14.0$, 1 H); 2.85 (*d*, $J = 14.0$, 1 H); 3.57 (br. *q*, $J = 5.2$, 2 H); 3.66 (*s*, 3 H); 4.00 (*t*, $J = 5.1$, 2 H); 4.12 (*q*, $J = 7.0$, 2 H); 5.10 (br. *t*, $J = 5.2$, NH); 6.78 (*m*, 2 H); 7.00 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 125.7 MHz): 14.59, 20.74, 26.68, 28.91, 29.86, 35.61, 39.45, 39.76, 40.52, 51.64, 52.02, 60.93, 66.99, 114.14, 129.67, 131.55, 157.23, 173.88, 214.14. MS: 405 (7, M^+), 107 (100). Anal. calc. for $C_{22}H_{31}NO_6$ (405.49): C 65.16, H 7.71; found ((*S*)-**12**): C 64.95, H 7.82; found ((*R*)-**12**): C 65.33, H 7.56; found ((*RS*)-**12**): C 64.89, H 7.67.

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Received April 16, 1998