# Efficient Palladium-Catalyzed Substitution in Enantiomerically Pure Allyl Carbonates − A Stereodivergent Access to β-Aryl-Substituted γ-Lactones and γ-Hydroxy Amides

**Manfred Braun*, Claudia Unger, and Kersten Opdenbusch**

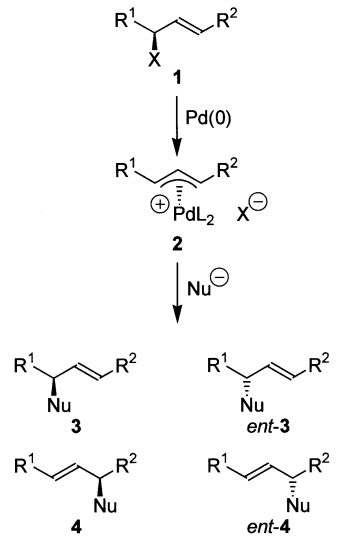
Institut für Organische Chemie und Makromolekulare Chemie, Universität Düsseldorf
Universitätsstraße 1, D-40225 Düsseldorf, Germany
Fax: (internat.) +49 (0) 211/81–13085
E-mail: braunm@uni-duesseldorf.de

Received July 3, 1998

**Keywords:** Palladium / Asymmetric synthesis / Allyl complexes / Chirality / Isomerizations

Allyl carbonates (*Z*)-**8** and (*E*)-**9** are available from the addition of the chiral alkenyllithium reagent **5b** to aromatic aldehydes **6**. When sujected to a palladium-catalyzed substitution by sodium malonate, (*Z*)-carbonates **8** give diesters **10** and **11**, whereas (*E*)-carbonate **9** predominantly leads to the diastereomeric product **12**. The latter is converted into (*S*)-γ-butyrolactone **13** in a three step sequence. When the same protocol is applied to the isomeric diesters **10** and **11**, (*R*)-lactones **13** result. A rationale for the stereochemical outcome of the allylic substitutions in the carbonates **10–12** is offered, based on π-σ-π interconversions of the palladium complexes **20–23**.

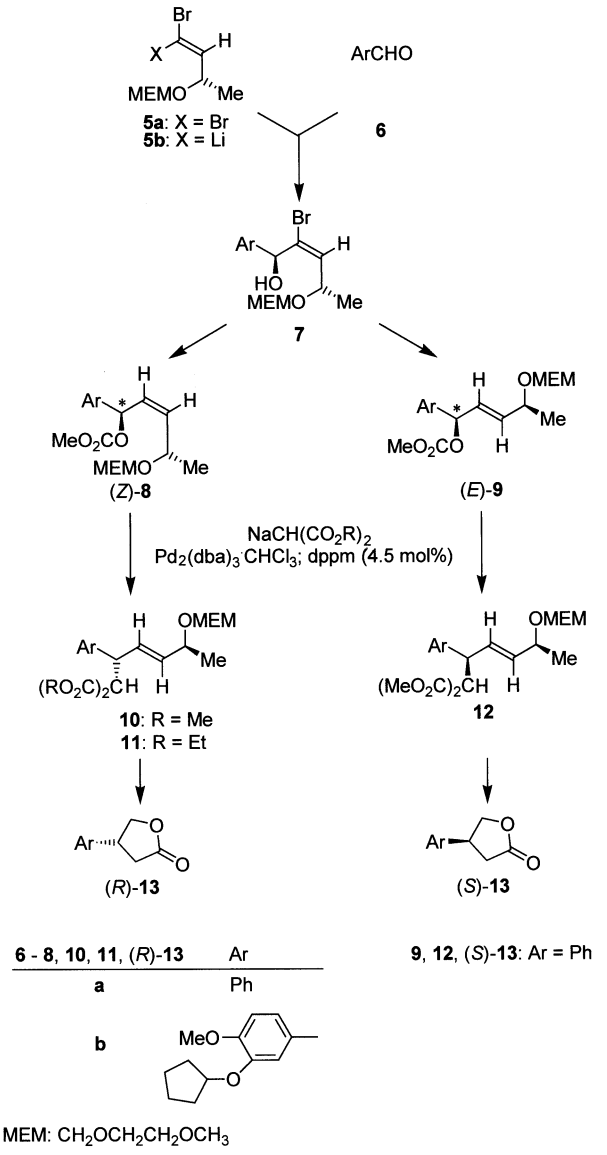
Transition-metal-catalyzed nucleophilic displacements on allylic substrates, introduced more than two decades ago, have proven their synthetic utility in numerous applications.[1] An especially efficient way of carbon−carbon bond formation was opened by the reaction of carbon nucleophiles with allyl palladium complexes whose in-situ generation usually requires only catalytic amounts of the transition metal.[2] Detailed mechanistic studies attended to the problems of regiochemistry and stereochemistry.[3] In principle, the regioisomers **3** and/or **4** can be formed, when unsymmetrically substituted allyl compounds **1** are subjected to the palladium-catalyzed substitution. On the other hand, those substrates **1** lead to the formation of allyl palladium complexes **2** with planar chirality, so that the possibility of chirality transfer is opened upon the addition of nucleophiles to the intermediates **2**. Depending mainly on the substitution pattern and the type of the nucleophile, either overall retention or inversion occurs. Thus, soft carbon nucleophiles usually attack the allyl complex **2** at the face opposite of the transition metal. Since the leaving group in **1** is also replaced by a rear side attack of the transition metal, an overall retention takes places in the sequence going from substrate **1** to the products **3** or **4**. On the other hand, hard nucleophiles which have rather seldom been used in this context, are believed to precoordinate to the palladium atom so that overall retention occurs affording *ent*-**3** or *ent*-**4**.[4] Enantioselectivity has been brought about in modern variants of the palladium-catalyzed allylic substitution. It relies in most cases on chiral ligands L attached to the palladium metal.[5] This fruitful approach is restricted mostly to racemic precursors **1** with identical substituents $R^1 = R^2$, whereas approaches which address themselves to the problem of regioselectivity as well as enantioselectivity are rare.[5f,h]




The approach presented in this paper[6] is based on a transfer of chirality from enantiomerically pure allylic substrates (*Z*)-**8** and (*E*)-**9** through allyl palladium complexes. In a highly diastereoselective manner, it leads to the formation of malonates **10**/**11** and **12**, respectively which are converted into enantiomeric γ-lactones (*R*)-**13** and (*S*)-**13**. As the alkenes (*Z*)-**8** and (*E*)-**9** are accessible from the addition of a single chiral reagent, (*S*)-**5,** to aromatic aldehydes **6**, this sequence evidently shows stereodivergent character.

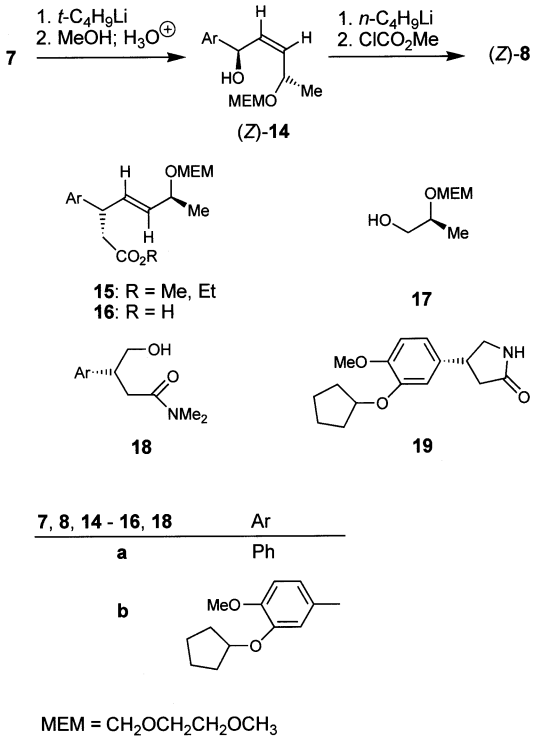
As described previously,[7] the chiral alkenyllithium reagent **5b** was generated at −105°C in diethyl ether from

  1434−193X/98/1111−2389 $ 17.50+.50/0 




dibromoalkene **5a** by slow addition of *n*-butyllithium. Subsequent dilution with tetrahydrofuran and addition of the aldehyde **6** led to the formation of the carbinols **7a** and **7b** which were obtained in > 99% *e.e.* and > 98% *d.e.* When the bromoalkenes **7** were subjected to another bromine/lithium exchange reaction and subsequently protonated, the allylic alcohols **14** resulted as pure (*Z*)-isomers.[7a] They were converted into the carbonates (*Z*)-**8** by protection of the hydroxy group and allowed to react with sodium malonate under palladium catalysis. Various complexes of the transition metal were applied to this conversion in order to find out their influence on the distribution of regioisomeric and stereoisomeric products. Finally, the combination of palladium dibenzylidene acetone $[Pd_2(dba)_3 \cdot CHCl_3]$[8] and bis(diphenylphosphinomethane) (dppm) turned out to be the most efficient system, leading to the diester **11a** which was obtained from (*Z*)-**8** as a single product in 96% yield. Remarkably, the formation of regioisomers was not observed under those conditions. The (*Z*/*E*) isomerization which occurred in the course of this reaction was proven unambiguously by the coupling constants of the vinylic protons in the $^1$H-NMR spectra. In a two-step sequence, which involved dealkoxycarbonylation (NaCN/LiI·3 $H_2O$; DMF/$H_2O$),[9] and saponification (LiOH; EtOH/$H_2O$), the carboxylic acid **16a** was available from **11a**. The yields obtained in these and analogous conversions (see below) are given in Table 1.

Ozonolysis of the olefinic double bond followed by reduction with sodium borohydride afforded the γ-lactone (*R*)-**13** in > 98% *e.e.* besides the MEM-protected propanediol **17** which may serve as starting material for the regeneration of the dibromoalkene **5a**. The absolute configuration of the lactone **13a**, which delivered the amide (*R*)-**18a** upon treatment with dimethylamine, was shown to be (*R*) by comparison of optical rotation.[10] This result clearly proved that the key step, the palladium-catalyzed conversion of the carbonate (*Z*)-**8a** into the diester **11a**, took place under inversion at *C. Analogously, the dimethyl ester **10a** was prepared from the carbonate (*Z*)-**8a** and converted into the carboxylic acid **16a** as well. However, the optimum route from (*Z*)-**8a** via the diethyl ester **11a** provided the lactone (**R**)-**13a** in 64% overall yield.




By the same procedure, the carbonate (*Z*)-**8b** was treated with sodium malonate to give (*E*)-alkene **10b** in 88% *d.e.* Without separation of the minor diastereomer, it was converted into the lactone **13b** in a sequence analogous to that outlined for **13a**. Thus, γ-butyrolactone **13b** was obtained in 87% *e.e.* In order to prove the enantiomeric excess, the heterocycle **13b** was opened by an aminolysis with dimethylamine. When investigated by $^1$H-NMR spectroscopy with the chiral shift reagent Eu(hfc)$_3$, the amide **18b** thus ob-

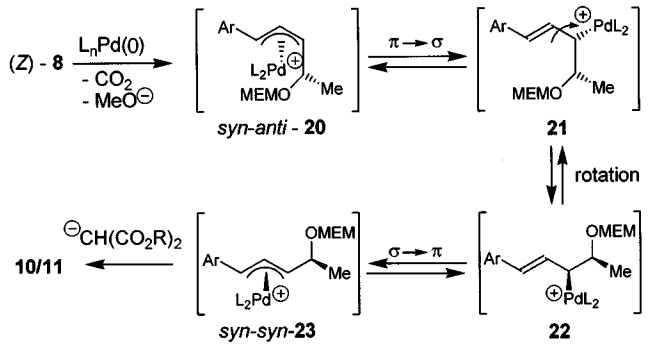
Table 1. Yields of alkenyl bromides **7**, alcohols **14** and **24**, carbonates **8** and **9**, malonates **10**-**12**, carboxylic acids **16** and **26**, and amides **18**

| Compound | Yield | Compound | Yield |
|---|---|---|---|
| **7a** | 93% | **11a** | 97% |
| **7b** | 90% | **11b** | 92% |
| **14a** | 94% | **12** | 56% |
| **14b** | 86% | **16a** | 96%[a] |
| **24** | 69% | **16b** | 53%[b] |
| **8a** | 98.5% | **16b** | 91%[c] |
| **8b** | 98% | **26** | 58%[d] |
| **9** | 95% | **18a** | 98% |
| **10a** | 50% | **18b** | 92% |
| **10b** | 77% | | |

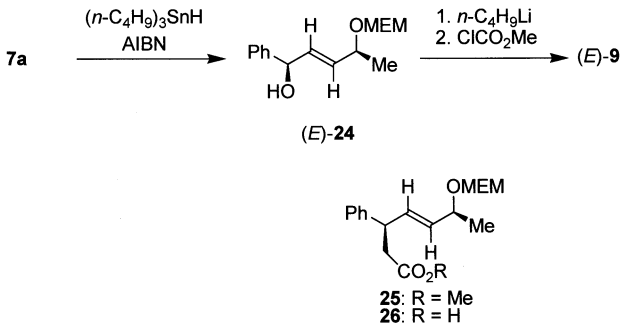
[a] Prepared from **11a**. – [b] Prepared from **10b**. – [c] Prepared from **11b**. – [d] Prepared from **12**.

tained showed 87% *e.e.* Since the lactone **13b** had previously been converted[11] into the antidepressant Rolipram® **19**,[12] the route outlined here can be considered to be a synthesis of the drug.[13] On an optimized route the diethyl ester **11b**, available in 90% *d.e.*, was converted into the lactone **13b** via the acid **16b** in 44% yield from (*Z*)-**8b**.

At a glance, the inversion at *C which turned out to be the overall stereochemical outcome found in the conversion of carbinols (*Z*)-**8** into diesters **10** and **11**, seemed surprising. Indeed, palladium-mediated allylic substitutions performed with soft nucleophiles (like deprotonated malonates) usually occur under net retention. Taking into account, however, the possibility of π-σ-π interconversions, as proposed by Hayashi,[3] a rationale of the net inversion can be offered as follows: It is assumed that in the first step, the allyl complex *syn-anti*-**20** is formed from the carbonate (*Z*)-**8** by a substitution under inversion. Subsequently, a rotation about the carbon-carbon double bond is effected by π-σ-π interconversion via the rotameric complexes **21** and **22**. Thereby, the palladium switches from the rear side in the *syn-anti*-diastereomer **20** to the front side in *syn-syn*-**23**. The final displacement of the palladium by the malonate anion occurs again under inversion so that the diastereomers **10**/**11** form exclusively or at least predominantly. Thus, it is a sequence of i) inversion, ii) rotation, and iii) inversion that causes the net inversion. The thermodynamically favored transformation of a *syn-anti* pattern in **20** into a *syn-syn*-**23** arrangement undoubtedly functions as the driving force for the π-σ-π interconversion.




There would be no need for a rotation, however, if the olefinic double bond in the substrate already had (*E*) configuration. This hypothesis was proven as follows. Whereas vinyllithium reagents are known to be configurationally stable when kept at low temperatures,[14] vinyl radicals usually isomerize spontaneously so that the more stable isomer forms.[15] Thus, the debromination of the alcohol **7a** was performed with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile. As expected, the radical mechanism induced by these reagents led to the formation of the thermodynamically favored (*E*)-alkene **24** exclusively. This is, again, clearly shown by the coupling constants of the alkenyl protons in the $^1$H-NMR spectrum. When the carbonate (*E*)-**9**, generated by protection of the allylic alcohol (*E*)-**24** was submitted to the palladium-catalyzed substitution with sodium malonate, the resulting main product **12** turned out to be a diastereomer of **10a**. A smaller amount of the latter compound was also formed, the diastereomeric ratio of **12**/**10a** being 92:8. The structure of the main product **12** was proven again by conversion into β-phenyl-γ-butyrolactone **13**. Thus, dealkoxycarbonylation of the diastereomeric mixture **12**/**10a** gave the methyl ester **25**, which was purified by column chromatography. The crystalline product **25** thus obtained was found to be free of its diastereomer **15a** (R = Me) according to the $^1$H-NMR spectrum. Subsequent hydrolysis, ozonolysis of the crude acid **26** thus formed and reduction afforded the lactone **13** in > 98% *e.e.* Since its configuration turned out to be (*S*) according to the optical rotation, both the structure of the main diastereomer **12** and, as a consequence, the overall retention at *C in the palladium-catalyzed substitution of carbonate (*E*)-**9** were proven.




On the one hand, the reaction sequences described here confirmed the mechanism which involves π-σ-π interconversions. On the other hand, a route was opened which started from single stereoisomers **7**, themselves available by an asymmetric synthesis, and led to the formation of enantiomeric products (*R*)- or (*S*)-**13** in a stereodivergent manner. It deserves to be mentioned that the target lactones (*R*)- and (*S*)-**13** were accessible in a controlled and predictable manner, due to an insight into the mechanism of the palladium-catalyzed allylic substitution.

This work was supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*. We would like to thank Dr. *A. Steigel*, Mrs. *M. Beuer*, Mrs. *I. Menzel* and Mr. *G.*

*Broszeit* for recording the spectra. A sample of (*R*)-Rolipram® was kindly provided by Dr. *R. Bohlmann* (Schering AG, Berlin).

## Experimental Section

Melting points (uncorrected): Büchi 510. − IR: Perkin-Elmer 1420 and Bruker NIR Vector 22. − NMR: Varian EM 360 A and VXR 300. All spectra were recorded in $CDCl_3$ with TMS as internal standard. In the $^{13}C$-NMR spectra, only selected, characteristic chemical shifts are given. − MS: Varian MAT CH-5, MAT 95 and MAT 8200. − Specific rotations: Perkin-Elmer 341. − TLC: DC-Alufolien Sil-60G/$UV_{254}$ (Merck). − CC: Kieselgel 60, mesh size 0.04−0.063 mm (Merck). − Elemental analyses: Mikroanalytisches Laboratorium Beller (Göttingen) and Institut für Pharmazeutische Chemie (Universität Düsseldorf).

*Solvents and Reagents:* Tetrahydrofuran (THF) and diethyl ether were predried with KOH and distilled under nitrogen from sodium/benzophenone. They were taken from the receiving flask, which was closed by a septum, with syringes or cannulas. Dichloromethane, chloroform, and *n*-hexane were refluxed for several hours with $P_2O_5$, distilled, and kept over molecular sieves (4 Å). Benzaldehyde was distilled before use. Neat diisobutylaluminium hydride (DIBAH), purchased from Aldrich, was diluted with *n*-hexane to give a 2 M solution. Methanol was refluxed with magnesium turnings (5 g/l), distilled and stored over molecular sieves (4 Å). The organolithium compounds *n*- and *tert*-butyllithium were purchased as solutions in *n*-hexane and *n*-pentane, respectively.

*General Remarks Concerning the Handling of Organolithium Compounds:* See ref.[16].

*(3S)-1,1-Dibromo-3-[(2-methoxyethoxy)methoxy]-1-butene* (**5a**) was prepared according to ref.[7a]

*3-Cyclopentyloxy-4-methoxybenzaldehyde* (**6b**) was prepared in 97% yield from commercially available isovanilline.[11][12]

*(1S,2E,4S)-2-Bromo-4-[(2-methoxyethoxy)methoxy]-1-phenyl-2-penten-1-ol* (**7a**) was prepared from benzaldehyde **6a** (12.7 g, 120 mmol) and **5a** (31.8 g, 100 mmol) according to ref.[7a]. Yield: 93% (31.2 g).

*(1S,2E,4S)-2-Bromo-1-(3-cyclopentyloxy-4-methoxyphenyl)-4-[(2-methoxyethoxy)methoxy]-2-penten-1-ol* (**7b**): A solution of **5a** (3.18 g, 10.0 mmol) in 50 ml of absolute diethyl ether was stirred at −108°C under nitrogen in a 100-ml two-necked flask equipped with a magnetic stirrer, a septum, and a connection to a combined nitrogen/vacuum line. A thermocouple was introduced through the septum, and *n*-butyllithium (6.0 ml of a 1.6 M solution in *n*-hexane, 9.6 mmol) was added slowly to the vigorously stirred mixture by means of a cannula. During the course of the addition, the temp. monitored by an electronic thermometer was not allowed to exceed −105°C. An excess of butyllithium was carefully avoided. A fine white precipitate formed gradually during the addition of *n*-butyllithium. After stirring for 15 min at −105°C, another 0.25-ml portion (0.4 mmol) of butyllithium solution was added and stirring was continued for 20 min at −105°C in order to complete the formation of **5b**.

The mixture was diluted with 2 ml of THF at −110°C, stirring was continued for 1 min, and a precooled solution of the aldehyde **6b** (2.42 g, 11.0 mmol) in THF (25 ml) was added through a cannula at such a rate that the temp. did not exceed −105°C. After stirring for 2 h at the same temp., the solution was allowed to reach −78°C within 90 min. A satd. aqueous solution of $NH_4Cl$ (10 ml) was added, and the cooling bath was removed so that the mixture could reach room temp. The organic layer was separated, the aqueous phase was diluted with water (20 ml) and extracted four times with a total amount of 100 ml of diethyl ether. The combined organic layers were washed with a satd. aqueous solution of $NH_4Cl$ (50 ml) and with brine (50 ml) and dried with $MgSO_4$. The solvent was removed in a rotary evaporator and the residue was exposed to vacuum (oil pump) for several h at room temp. The crude product **7b** thus obtained was free of other diastereomers according to the $^1H$ NMR spectrum. CC (*n*-hexane/ethyl acetate/chloroform, 1:2:1) afforded 4.12 g (90%) of colorless, viscous **7b**, *d.e.* > 98%, $R_f$ = 0.73, $[\alpha]_D^{20}$ = −175.9 (*c* = 1.3 in 95% aqueous ethanol). − $^1H$ NMR (300 MHz): δ = 1.32 (d, *J* = 6.4 Hz, 3 H, $CH_3$), 1.75 [m, 8 H, $(CH_2)_4$], 3.36 (s, 3 H, $CH_2OCH_3$), 3.62 (m, 4 H, $OCH_2$-$CH_2O$), 3.83 (s, 3 H, $ArOCH_3$), 4.75 (AB system, $J_{AB}$ = 7.1 Hz, 2 H, $OCH_2O$), 4.78 [m, 1 H, C*H*(OH)], 4.94 [dq, $J_d$ = 8.9 Hz, $J_q$ = 6.4 Hz, 1 H, C*H*(O-)$CH_3$], 5.59 (d, *J* = 6.2 Hz, 1 H, OH), 6.03 (d, *J* = 9.2 Hz, 1 H, HC=CBr), 6.86 (m, 3 H, aromatic H). − MS (70 eV); *m*/*z* (%): 460, 458 (2) [$M^+$], 355, 353 (6) [$M^+ - C_4H_9O_3$], 89 (62) [$C_4H_9O_2$], 59 (100) [$C_3H_7O$]. − $C_{21}H_{31}BrO_6$ (459.4): calcd. C 54.91, H 6.80; found C 54.93, H 6.87.

*(1R,2Z,4S)-4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-penten-1-ol* (**14a**) was prepared from **7a** (11.1 g, 32.1 mmol) according to ref.[7a]. Yield: 8.01 g (94%).

*(1R,2Z,4S)-1-(3-Cyclopentyloxy-4-methoxyphenyl)-4-[(2-methoxyethoxy)methoxy]-2-penten-1-ol* (**14b**): A solution of **7b** (4.0 g, 8.7 mmol) in THF (20 ml) was stirred under nitrogen at −105°C in a 250-ml two-necked flask equipped with a stirring bar, a connection to the combined nitrogen/vacuum line, and a thermocouple which was introduced through a septum. A 1.5 M solution of *tert*-butyllithium in pentane (2.1 ml, 3.2 mmol) was added to the vigorously stirred solution at such a rate that the temp. did not exceed −95°C. The mixture, which turned orange, was allowed to reach −30°C within 1 h. After cooling to −78°C, methanol (3 ml) and a satd. aqueous solution of $NH_4Cl$ was added. Thereafter, the mixture was poured into diethyl ether (100 ml) and the organic layer was separated. The aqueous layer was extraced with three 20-ml portions of diethyl ether. The combined organic layers were washed with brine (30 ml) and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by CC (*n*-hexane/ethyl acetate/chloroform, 1:3:1) to yield 2.85 g (86%) of colorless, viscous **14b**; $R_f$ = 0.65, $[\alpha]_D^{20}$ = −206 (*c* = 1.3 in 95% aqueous ethanol). − $^1H$ NMR (300 MHz): δ = 1.31 (d, *J* = 6.3 Hz, 3 H, $CH_3$), 1.60 and 1.90 [2 m, 8 H, $(CH_2)_4$], 2.47 (d, *J* = 3.3 Hz, 1 H, OH), 3.37 (s, 3 H, $CH_2OCH_3$), 3.65 (m, 4 H, $OCH_2$-$CH_2O$), 3.82 (s, 3 H, $ArOCH_3$), 4.65 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 4.79 [m, 1 H, CH(O-)], 4.89 dq ($J_d$ = 8.6 Hz, $J_q$ = 6.3 Hz, 1 H, C*H*(O-)$CH_3$], 5.58 [m, 3 H, vinyl H and C*H*(OH)], 6.90 (m, 3 H, aromatic H). − MS (70 eV); *m*/*z* (%): 381 (10) [$M^+$ + 1], 275 (100) [$M^+ - C_4H_9O_3$], 272 (20) [$M^+ - C_4H_{12}O_3$], 206 (43) [$C_{12}H_{14}O_3$], 191 (20) [$C_{12}H_{15}O_2$], 189 (55) [$M^+ - C_{12}H_{15}O_2$], 151 (34) [$C_8H_7O_3$], 59 (38) [$C_3H_7O$]. − $C_{21}H_{32}O_6$ (380.6): calcd. C 66.28, H 8.48; found C 66.31, H 8.65.

*(1R,2E,4S)-4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-penten-1-ol* (**24**): A 50-ml two-necked flask was equipped with a reflux condenser with a connection to the combined nitrogen/vacuum line and a magnetic stirrer, charged with **7a** (0.50 g, 1.45 mmol), and closed with a septum. The air in the flask was replaced by nitrogen, and benzene (19.4 ml) and tri-*n*-butyltin hydride (0.77 ml, 2.92 mmol) were injected by syringes. Azobisisobutyronitrile (10.2 mg, 0.06 mmol) was added while removing the septum briefly and the mixture was refluxed for 7 h. Another portions of tri-*n*-butyltin hydride and azobisisobutyronitrile (same quantities as above) were added, and refluxing was continued for another 7 h. Thereafter, the

solvent was removed by distillation, the residue was dissolved in diethyl ether (20 ml), and a 10% aqueous solution of KF (20 ml) was added. The white precipitate formed thereby was filtered and washed with diethyl ether (100 ml). The combined filtrates were dried with $MgSO_4$, and the solvent was removed in a rotary evaporator. The residue was purified by CC (*n*-hexane/ethyl acetate/chloroform, 1:3:1) to give 0.266 g (69%) of colorless, oily **24**; $R_f$ = 0.53, $[\alpha]_D^{20}$ = −88.8 (*c* = 1.08 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.26 (d, *J* = 6.5 Hz, 3 H, $CH_3$), 2.67 (d, *J* = 3.7 Hz, 1 H, OH), 3.37 (s, 3 H, $OCH_3$), 3.61 (m, 4 H, $OCH_2$-$CH_2O$), 4.21 [(m, 1 H, CH(O-)], 4.73 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 5.17 [dd, *J* = 5.8 Hz, *J* = 3.6 Hz, 1 H, C*H*(OH)], 5.72 [dd, *J* = 16.0 Hz, *J* = 6.0 Hz, 1 H, CH(OH)CH=C*H*], 5.86 [dd, *J* = 16.0 Hz, *J* = 5.8 Hz, 1 H, CH(OH)C*H*=CH], 7.33 (m, 5 H, aromatic H).

*General Procedure for the Conversion of Alcohols* **14a**, **b** *and* **24** *into Carbonates* **8** *and* **9**: A 100-ml two-necked flask was equipped with a magnetic stirrer, connected to the combined nitrogen/vacuum line, charged with 6.5 mmol of the alcohol **14a**, **b**, or **24**, and closed with a septum. The air in the flask was replaced by nitrogen, and 50 ml of diethyl ether were injected. The mixture was cooled to −78°C and a 1.6 M solution of *n*-butyllithium (4.5 ml, 7.2 mmol) was added slowly by syringe. Stirring was continued for 20 min and methyl chloroformate (0.65 ml, 8.43 mmol) was injected. Thereafter, the mixture was allowed to reach 0°C within 3 h, and a white precipitate formed gradually. A satd. aqueous solution of $NH_4Cl$ (20 ml) was added, and the mixture was transferred into a separatory funnel. The organic layer was separated and the aqueous phase was extracted three times with a total amount of 120 ml of ethyl acetate. The combined organic layers were dried with $MgSO_4$ and the solvent was removed in a rotary evaporator. The crude product thus obtained was either submitted to CC or used without purification in the next step.

According to this procedure, the following were obtained:

*Methyl (8S,9Z,11R)-8-Methyl-11-phenyl-2,5,7,12-tetraoxatridec-9-en-13-oate* (*Z*)-**8a**: Prepared from (*Z*)-**14a** (1.6 g, 60 mmol) and purified by CC (ethyl acetate/chloroform, 1:1); $R_f$ = 0.86. Yield: 1.92 g (98.5%) of colorless oily (*Z*)-**8a**; $[\alpha]_D^{20}$ = −154.5 (*c* = 1.95 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.34 (d, *J* = 6.3 Hz, 3 H, $CH_3$), 3.38 (s, 3 H, $CH_2OCH_3$), 3.65 (m, 4 H, $OCH_2CH_2O$), 3.77 [s, 3 H, $C(O)OCH_3$], 4.63 (s, 2 H, $OCH_2O$), 4.85 [dq, $J_d$ = 9.2 Hz, $J_q$ = 6.3 Hz, 1 H, C*H*(O-)$CH_3$], 5.59 (m, 2 H, HC=CH), 6.43 [d, *J* = 9.5 Hz, 1 H, C*H*OC(O)$OCH_3$], 7.37 (m, 5 H, aromatic H). − MS (70 eV); *m*/*z* (%): 219 (19) [$M^+ - C_4H_9O_3$], 218 (61) [$M^+ - C_4H_{10}O_3$], 143 (56) [$C_{11}H_{11}$], 89 (100) [$C_4H_9O_2$]. − $C_{17}H_{24}O_6$ (324.4): calcd. C 62.94, H 7.46; found C 62.98, H 7.42.

*Methyl (8S,9Z,11R)-11-[3-(Cyclopentenyloxy)-4-methoxyphenyl]-8-methyl-2,5,7,12-tetraoxatridec-9-en-13-oate* (*Z*)-**8b**: Prepared from **13b** (2.78 g, 7.3 mmol) and used without purification because decomposition was observed upon CC. Crude yield: 3.14 g (98%). − $^1$H NMR (300 MHz): δ = 1.33 (d, *J* = 6.3 Hz, 3 H, $CH_3$), 1.75 [m, 8 H, $(CH_2)_4$], 3.38 (s, 3 H, $CH_2OCH_3$), 3.55 (m, 4 H, $OCH_2$-$CH_2O$), 3.77 [s, 3 H, $C(O)OCH_3$], 3.83 (s, 3 H, $ArOCH_3$), 4.61 (s, 2 H, $OCH_2O$), 4.83 [m, 2 H, C*H*(O)$CH_3$ and CH(O-)], 5.63 (m, 2 H, HC=CH), 6.35 [d, *J* = 8.3 Hz, 1 H, C*H*OC(O)$OCH_3$], 6.90 (m, 3 H, aromatic H). − MS (70 eV); *m*/*z* (%): 395 (37) [$M^+ - C_2H_3O$], 288 (100) [$C_{17}H_{20}O_4$], 274 (23) [$C_{17}H_{22}O_3$], 261 (40) [$C_{14}H_{13}O_5$], 205 (67) [$C_{13}H_{17}O_2$], 203 (29) [$C_{13}H_{15}O_2$], 175 (30) [$C_{11}H_{11}O_2$], 89 (38) [$C_4H_9O_2$], 59 (90) [$C_3H_7O$].

*Methyl (8S,9E,11R)-8-Methyl-11-phenyl-2,5,7,12-tetraoxatridec-9-en-13-oate* (*E*)-**9**: Prepared from (*E*)-**24** (0.375 g, 1.41 mmol) and used without purification. Crude yield: 0.43 g (95%). − $^1$H NMR (300 MHz): δ = 1.25 (d, *J* = 6.4 Hz, 3 H, $CH_3$), 3.38 (s, 3 H, $CH_2OCH_3$), 3.52 (m, 4 H, $OCH_2CH_2O$), 3.77 [s, 3 H, $C(O)OCH_3$], 4.70 [m, 3 H, $OCH_2O$ und C*H*(O-)$CH_3$], 5.71 [m, 1 H, HC=C*H*CH$(CH_3)$], 5.86 [m, 1 H, *H*C=CHCH$(CH_3)$], 6.07 [d, *J* = 5.8 Hz, 1 H, C*H*OC(O)$OCH_3$], 7.32 (m, 5 H, aromatic H).

*General Procedure for the Conversion of Carbonates* (*Z*)-**8** *and* (*E*)-**9** *into Malonates* **10**−**12**: A 25-ml flask equipped with a septum, a magnetic stirrer, and a connection to the combined nitrogen/vacuum line was charged with an 80% dispersion of NaH in mineral oil (0.055 mg, 1.9 mmol). *n*-Hexane (10 ml) was injected and the suspension was stirred for several min. Stirring was stopped, and the supernatant solvent was removed by syringe. This process was repeated four times. Thereafter, the flask was evacuated in order to remove the residual hexane. THF (5 ml) was added and the suspension was cooled to −5°C. Under stirring, diethyl or dimethyl malonate (2.0 mmol) was added dropwise by syringe, and the mixture was allowed to reach room temp.

In a second 25-ml flask, a solution of the corresponding carbonate **8** or **9** (1.0 mmol) in THF (3 ml) was stirred under nitrogen, and $Pd_2(dba)_3 \cdot CHCl_3$ (0.045 g, 0.045 mmol) as well as bis(diphenylphosphino)methane (0.14 g, 0.36 mmol) were added. After stirring for 10 min at room temp., the solution of sodium malonate prepared as described above was added slowly through a cannula. Thereafter, the mixture was stirred in a water bath (35°C) for 4 h, and stirring was continued overnight at room temp. A satd. aqueous solution of $NH_4Cl$ (10 ml) was added, and the mixture was transferred into a separating funnel. Diethyl ether (20 ml) was added and the organic phase was separated. The aqueous phase was extracted three times with diethyl ether (70 ml), the combined organic layers were dried with $MgSO_4$ and the solvent was removed in a rotary evaporator. The crude product was purified by CC.

According to this procedure, the following were obtained:

*Dimethyl (1′R,2′E,4′S)-{4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-pentenyl}propanedioate* (**10a**): Prepared from (*Z*)-**8a** (1.09 g, 3.36 mmol) by reaction with sodium dimethylmalonate. The crude product was purified by CC (*n*-hexane/ethyl acetate/chloroform, 4:2:1) to give 0.64 g (50%) of colorless, oily **10a** as a single diastereomer; $R_f$ = 0.48; $[\alpha]_D^{20}$ = −44.4 (*c* = 1.24 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.20 (d, *J* = 6.5 Hz, 3 H, $CH_3$), 3.35 (s, 3 H, $CH_2OCH_3$), 3.56 (m, 4 H, $OCH_2CH_2O$), 3.49 and 3.72 [2s, 3 H each, $(CO_2CH_3)_2$], 4.12 [m, 2 H, CH(Ar) and C*H*(O-)$CH_3$], 4.61 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 5.46 [dd, *J* = 15.4 Hz, *J* = 7.5 Hz, 1 H, HC=C*H*CH$(CH_3)$], 5.81 [dd, *J* = 15.4 Hz, *J* = 8.5 Hz, 1 H, *H*C=CHCH$(CH_3)$], 7.20 (m, 5 H, aromatic H). − $^{13}$C NMR (75 MHz): δ = 21.5 (C-5′), 48.5 (C-1′), 52.4 and 52.5 $(CO_2CH_3)_2$, 57.6 (C-2), 59.0 (C-4′′), 66.7 (C-2′′), 71.7 (C-3′′), 72.0 (C-4′), 92.7 (C-1′′) 127.1 (aromatic *p*-H), 127.8 (aromatic *o*-H), 128.6 (aromatic *m*-H), 131.5 (C-3′), 133.7 (C-2′), 140.0 (aromatic *ipso*-H), 167.7 and 168.0 (C-1, C-3). − MS (70 eV); *m*/*z* (%): 320 (2) [$M^+ - C_2H_4O_2$], 276 (9) [$M^+ - C_4H_8O_3$], 275 (5) [$M^+ - C_4H_9O$], 249 (19) [$M^+ - C_5H_7O_4$], 215 (8) [$M^+ - C_6H_{13}O_5$], 214 (12) [$M^+ - C_6H_{14}O_5$], 191 (7) [$C_8H_{15}O_5$], 159 (12) [$M^+ - C_{12}H_{13}O_4$], 144 (14) [$C_7H_{12}O_3$], 143 (18) [$C_7H_{11}O_3$], 89 (88) [$C_4H_9O_2$], 59 (100) [$C_2H_3O_2$]. − $C_{20}H_{28}O_7$ (380.4): calcd. C 63.14, H 7.42; found C 63.09, H 7.29.

*Diethyl (1′R,2′E,4′S)-{4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-pentenyl}propanedioate* (**11a**): Prepared from (*Z*)-**8a** (0.324 g, 1.0 mmol) and sodium diethyl malonate. The crude product was purified by CC (ethyl acetate/chloroform, 1:2) to give 0.395 g (97%) of colorless, oily **11a**. Both the crude and the purified products were obtained as single diastereomers; $R_f$ = 0.8; $[\alpha]_D^{20}$ = −49.7 (*c* = 1.05 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ =

0.98 and 1.27 (2 t, $J$ = 7.1 Hz, 3 H each, $CH_2CH_3$), 1.20 (d, $J$ = 6.5 Hz, 3 H, $CH_3$), 3.35 (s, 3 H, $OCH_3$), 3.60 (m, 4 H, $OCH_2CH_2O$), 3.80 [d, $J$ = 11.1 Hz, 1 H, $CH(CO_2C_2H_5)_2$], 3.93 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.08 [dd, $J_1$ = 11.1 Hz, $J_2$ = 8.3 Hz, 1 H, $CH$(Ph)], 4.16 [m, 1 H, $CH$(O-)$CH_3$], 4.18 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.59 (AB system, $J_{AB}$ = 6.9 Hz, 2 H, $OCH_2O$), 5.45 [dd, $J_1$ = 7.5 Hz, $J_2$ = 15.4 Hz, HC=$CH$CH($CH_3$)], 5.82 [dd, $J_1$ = 8.3 Hz, $J_2$ = 15.4 Hz, 1 H, $HC$=CHCH($CH_3$)], 7.23 (m, 5 H, aromatic H). − MS (70 eV); *m/z* (%): 333 (2) [$M^+ - C_3H_5O_2$], 319 (3) [$M^+ - C_4H_9O_2$], 303 (8) [$M^+ - C_4H_9O_3$], 248 (18) [$M^+ - C_7H_{12}O_4$], 89 (80) [$C_4H_9O_2$], 59 (100) [$C_2H_3O_2$]. − $C_{22}H_{32}O_7$ (408.5): Calcd. C 64.69, H 7.90; found C 64.61, H 7.75.

*Dimethyl [1′R,2′S,4′S]-{1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4-[(2-methoxyethoxy)methoxy]-2-pentenyl}propanedioate* (**10b**): Prepared from (*Z*)-**8b** (3.3 g, 7.5 mmol) by reaction with sodium dimethylmalonate. The diastereomeric excess was determined to be 88% *d.e.* according to the $^1$H-NMR spectrum of the crude product. Purification by CC (*n*-hexane/ethyl acetate/chloroform, 4:2:1) gave 2.87 g (77%) of colorless, oily **10b**; *d.e.*: 88%; $R_f$ = 0.4; $[\alpha]_D^{20}$ = −46.5 (*c* = 1.2 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.21 (d, $J$ = 6.4 Hz, 3 H, $CH_3$), 1.75 [m, 8 H, $(CH_2)_4$], 3.36 (s, 3 H, $OCH_3$), 3.59 (m, 4 H, $OCH_2CH_2O$), 3.51 and 3.72 [2 s, 3 H each, $(CO_2CH_3)_2$], 3.76 [d, $J$ = 8.5 Hz, 1 H, $CH(CO_2CH_3)_2$], 3.81 (s, 3 H, $ArOCH_3$), 4.00 [dd, $J_1$ = 8.2 Hz, $J_2$ = 8.5 Hz, 1 H, CH(Ar)], 4.15 [m, 1 H, $CH$(O-)$CH_3$], 4.63 (AB system, $J_{AB}$ = 6.9 Hz, 2 H, $OCH_2O$), 4.75 [m, 1 H, CH(O-)], 5.43 [dd, $J$ = 15.4 Hz, $J$ = 7.5 Hz,1 H, HC=$CH$CH($CH_3$)], 5.80 [dd, $J$ = 15.4 Hz, $J$ = 8.2 Hz, 1 H, $HC$=CHCH($CH_3$)], 6.76 (m, 3 H, aromatic H).

The $^1$H-NMR spectrum of the minor diastereomer differs from that of **10b** in: δ = 1.19 (d), 3,38 (5), 5.29 (m), 5.71 (m)

*Diethyl [1′R,2′S,4′S]-{1-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4-[(2-methoxyethoxy)methoxy]-2-pentenyl}propanedioate* (**11b**): Prepared from (*Z*)-**8b** (3.11 g, 7.1 mmol) by reaction with sodium diethylmalonate. The diastereomeric excess of the crude product was determined to be 90% *d.e.* according to the $^1$H-NMR spectrum. Purification by CC (ethyl acetate/chloroform, 1:2) gave 3.41 g (92%) of colorless, oily **11b**; $R_f$ = 0.9; $[\alpha]_D^{20}$ = −47.9 (*c* = 0.6 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.02 and 1.27 (2t, $J$ = 7.1 Hz, 3 H each, $CH_2CH_3$), 1.20 (d, $J$ = 6.5 Hz, 3 H, $CH_3$), 1.77 [m, 8 H, $(CH_2)_4$], 3.36 (s, 3 H, $OCH_3$), 3.60 (m, 4 H, $OCH_2CH_2O$), 3.74 [d, $J$ = 11.1 Hz, 1 H, $CH(CO_2C_2H_5)_2$], 3.81 (s, 3 H, $ArOCH_3$), 3.95 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.03 (dd, $J_1$ = 11.1 Hz, $J_2$ = 8.1 Hz, 1 H, $CH$Ar), 4.18 (q, $J$ = 7.1 Hz, 2 H, $CH_2CH_3$), 4.20 [m, 1 H, $CH$(O-)$CH_3$], 4.61 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 4.74 [m, 1 H, CH(O-)], 5.41 [dd, $J$ = 15 Hz, $J$ = 7.5 Hz, 1 H, CH=$CH$CH($CH_3$)], 5.79 [dd, $J$ = 15 Hz, $J$ = 8.1 Hz, 1 H, $HC$=CHCH($CH_3$)], 6.75 (m, 3 H, aromatic H). − MS (70 eV); *m/z* (%): 522 (28) [$M^+$], 348 (12) [$M^+ - C_9H_{18}O_3$], 189 (48) [$C_{12}H_{13}O_2$], 188 (71) [$C_{12}H_{12}O_2$], 133 (12) [$C_6H_{13}O_3$], 115 (24) [$C_5H_7O_3$], 59 (100) [$C_3H_7O$]. − $C_{28}H_{42}O_9$ (522.6): Calcd. C 64.35, H 8.10; found C 64.28, H 8.01.

The $^1$H-NMR spectrum of the minor diastereomer differs from that of **11b** in: δ = 1.00 and 1.27 (2 t), 1.19 (d), 3.38 (s).

*Dimethyl (1′S,2′E,4′S)-{4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-pentenyl}propanedioate* (**12**): Prepared from (*E*)-**9** (0.457 g, 1.41 mmol) by reaction with sodium dimethylmalonate. The diastereomeric ratio of **12**/**10a** was determined to amount to 92:8 according to the $^1$H-NMR and $^{13}$C-NMR spectra of the crude product. Purification by column chromatography (*n*-hexane/ethyl acetate/chloroform, 4:2:1) gave 0.302 g (56%) of colorless, oily **12**/**10a**, 92:8; $R_f$ = 0.34; $[\alpha]_D^{20}$ = −67.9 (*c* = 1.04 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 1.18 (d, $J$ = 6.4 Hz, 3 H, $CH_3$), 3.37 (s, 3 H, $OCH_3$), 3.58 (m, 4 H, $OCH_2CH_2O$), 3.48 and 3.73 [s, 3 H each, $(CO_2CH_3)_2$], 3.84 [d, $J$ = 11.1 Hz, 1 H, $CH(CO_2CH_3)_2$], 4.11 [m, 2 H, CHAr and $CH$(O-)$CH_3$], 4.65 (AB system, $J_{AB}$ = 6.9 Hz, 2 H, $OCH_2O$), 5.47 [dd, $J$ = 15.4 Hz, $J$ = 7.4 Hz, 1 H, HC=$CH$CH($CH_3$)], 5.81 [dd, $J$ = 15.4 Hz, $J$ = 8.5 Hz, 1 H, $HC$=CHCH($CH_3$)], 7.20 (m, 5 H, aromatic H). − $^{13}$C NMR (75 MHz): Differs from that of **10a** in: δ = 71.8 (C-4′), 92.5 (C-1′′).

*General Procedure for the Conversion of Malonates* **10**−**12** *into Carboxylic Acids* **16** *and* **26**: A solution of the corresponding malonate **10**−**12** (2.5 mmol), in dry *N,N*-dimethylformamide (27 ml) was treated with NaCN (0.124 g, 2.53 mmol) and LiI·3 $H_2O$ (2.57 g, 13.68 mmol). The mixture was heated to 140°C for 18 h. After cooling to room temp., diethyl ether (120 ml) was added. The solution was washed with water and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The crude esters **15a** (R = Et), **15b** (R = Me, Et) and **25** (R = Me) were subjected to CC (*n*-hexane/ethyl acetate/chloroform, 1:1:1) and used without further purification in the following step.

A solution of the methyl or ethyl esters **15** and **25** (R = Me, Et) (1.84 mmol) in ethanol (5 ml) was treated with a 0.5 M aqueous solution of lithium hydroxide (15 ml) and heated to 42−45°C for 4 h. The ethanol was removed for the most part in a rotary evaporator and the aqueous residue was brought to pH = 2 by addition of 2 M hydrochloric acid. Ethyl acetate (20 ml) was added and the mixture was transferred into a separating funnel. The organic layer was removed and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was removed in a rotary evaporator. The residual carboxylic acids were not purified but characterized by their $^1$H NMR spectra.

According to this procedure, the following were obtained:

*(3S,4E,6S)-6-[(2-Methoxyethoxy)methoxy]-3-phenyl-4-heptenoic Acid* (**16a**): Prepared from **11a** (0.38 g, 0.93 mml); yield: 0.275 g (96%). − $^1$H NMR (300 MHz): δ = 1.22 (d, $J$ = 6.4 Hz, 3 H, $CH_3$), 2.72 (d, $J$ = 7.7 Hz, 2 H, $CH_2CO_2H$), 3.36 (s, 3 H, $OCH_3$), 3.56 (m, 4 H, $OCH_2CH_2O$), 3.87 [m, 1 H, CH(Ph)], 4.18 [m, 1 H, CH(O-)$CH_3$], 4.65 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 5.40 [dd, $J$ = 14.0 Hz, $J$ = 7.5 Hz, 1 H, HC=$CH$CH($CH_3$)], 5.80 [dd, $J$ = 14.0 Hz, $J$ = 6.5 Hz, 1 H, $HC$=CHCH($CH_3$)], 7.25 (m, 5 H, aromatic H), 9.4 (broad s, 1 H, $CO_2H$).

*(1′E,3S,3′S)-3-(Cyclopentyloxy)-4-methoxy-3-{3-[(2-methoxyethoxy)methoxy]-1-butenyl}benzenepropanoic Acid* (**16b**): Prepared from **10b** (1.31 g, 2.65 mmol); yield: 0.60 g (53%); prepared from **11b** (3.2 g, 6.1 mmol); yield: 2.35 g (91%). − $^1$H NMR (300 MHz): δ = 1.25 (d, $J$ = 6.5 Hz, 3 H, $CH_3$), 1.5 and 1.9 [2m, 8 H, $(CH_2)_4$], 2.71 (d, $J$ = 8.5 Hz, 2 H, $CH_2CO_2H$), 3.38 (s, 3 H, $CH_2OCH_3$), 3.65 [m, 5 H, $OCH_2CH_2O$ and CH(Ar)], 3.82 (s, 3 H, $ArOCH_3$), 4.15 [m, 1 H, $CH$(O-)$CH_3$], 4.66 (AB system, $J_{AB}$ = 7.0 Hz, 2 H, $OCH_2O$), 4.74 [m, 1 H, CH(O-)], 5.42 [m, 1 H, HC=$CH$CH($CH_3$)], 5.79 (dd, $J$ = 15.6 Hz, $J$ = 6.9 Hz, 1 H, $HC$=CHCH($CH_3$)], 6.75 (m, 3 H, aromatic H), 9.45 (broad s, 1 H, $CO_2H$).

*(3R,4E,6S)-6-[(2-Methoxyethoxy)methoxy]-3-phenyl-4-heptenoic Acid* (**26**): Prepared from **12** (0.955 g, 2.51 mmol); yield: 0.45 g (58%). − $^1$H NMR (300 MHz): δ = 1.21 (d, $J$ = 6.4 Hz, 3 H, $CH_3$), 2.73 (d, $J$ = 7.7 Hz, 2 H, $CH_2CO_2H$), 3.38 (s, 3 H, $OCH_3$), 3.5 and 3.7 (2m, 4 H, $OCH_2CH_2O$), 3.84 [m, 1 H, CH(Ar)], 4.15 [m, 1 H, $CH$(O-)$CH_3$], 4.68 (AB system, $J_{AB}$ = 6.9 Hz, 2 H, $OCH_2O$), 5.44 [m, 1 H, HC=$CH$CH($CH_3$)], 5.79 [dd, $J$ = 15.5 7.6

Hz, $J$ = 7.6 Hz, 1 H, *H*C=CHCH($CH_3$)], 7.25 (m, 5 H, aromatic H), 8.55 (broad s, 1 H, $CO_2H$).

*General Procedure for the Preparation of γ-Butyrolactones* **13**: By means of a frit, a stream of ozone in $O_2$ was passed through a solution of the carboxylic acids **16** or **26** (1.66 mmol) in dichloromethane or methanol (50 ml) at −78°C until the blue color persisted. Thereafter, the mixture was treated with streams of $O_2$ and $N_2$ and was allowed to reach room temp. A solution of $NaBH_4$ (0.471 g, 12.45 mmol) in aqueous ethanol (1:1) was added and the mixture was stirred for 12 h. Another portion of $NaBH_4$ (0.205 g, 5.41 mmol) was added, and stirring was continued for 3 h. Thereafter, the mixture was concentrated in a rotary evaporator and the remaining aqueous solution was brought to pH = 0 by the addition of 2 M hydrochloric acid and stirred at 50°C for 4 h. After cooling to room temp., the solution was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in a rotary evaporator. The residue solidified and was purified by CC. According to this procedure, the following were obtained:

(*R*)-*4-Phenyldihydro-2(3H)-furanone* [(*R*)-**13a**]: Prepared from **16a** (0. 25 g, 0.81 mmol); yield: 0.090 g (69%); $R_f$ = 0.84 (*n*-hexane/ethyl acetate/chloroform, 1:2:1); m.p. 59°C [ref.[10b] 61−61.5°C for (*S*)-**13**]; $[\alpha]_D^{20}$ = −50.1 (*c* = 1.1 in absolute methanol) {ref[10b] $[\alpha]_D^{20}$ = −50 (*c* = 4.7 in methanol)}; {ref.[10a] $[\alpha]_D^{28}$ = 51 (*c* = 8.6 in ethanol) for (*S*)-**13**}. − $^1$H NMR (300 MHz): δ = 2.67 (dd, $J_{1,1}$ = 17.5 Hz, $J_{1,2}$ = 9.2 Hz, 1 H, 3-H), 2.92 (dd, $J_{1,1}$ = 17.5 Hz, $J_{1,2}$ = 8.7 Hz, 1 H, 3-H), 3.79 (quint., $J$ = 8.4 Hz, 1 H, 4-H), 4.27 (dd, $J_{1,1}$ = 9.0 Hz, $J_{1,2}$ = 8.0 Hz, 1 H, 5-H), 4.67 (dd, $J_{1,1}$ = 9.0 Hz, $J_{1,2}$ = 7.9 Hz, 1 H, 5-H), 7.3 (m, 5 H, aromatic H).

(*S*).*4-Phenyl-dihydro-2(3H)-furanone* [(*S*)-**13a]**: Prepared from **26** (0.512 g, 1.66 mmol); yield: 0.238 g (88%); $[\alpha]_D^{20}$ = 52.8 (*c* = 1 in 95% aqueous ethanol).

(*R*)-*4-[3-(Cyclopentyloxy)-4-methoxyphenyl]dihydro-2[3H]-furanone* [(*R*)-**13b**]: Prepared from **16b** (0.66 g, 1.56 mmol); yield: 0.229 g (53%); $R_f$ = 0.81 (ethyl acetate/chloroform, 1:3); yellowish oil which solidified after several days; $[\alpha]_D^{20}$ = −28.1 (*c* = 1.0 in abs methanol) {ref.[11a] $[\alpha]_D$ = −32.4 (*c* = 0.6 in chloroform)} − $^1$H NMR (300 MHz): δ = 1.6 and 1.9 [2m, 8 H, $(CH_2)_4$], 2.65 (dd, $J_{1,1}$ = 17.5, $J_{1,2}$ = 9.1 Hz, Hz, 1 H, 3-H), 2.91 (dd, $J_{1,1}$ = 17.4 Hz, $J_{1,2}$ = 8.7 Hz, 1 H, 3-H), 3.72 (m, 1 H, 4-H), 3.83 (s, 3 H, Ar-$OCH_3$), 4.24 (dd, $J_{1,1}$ = 9.0 Hz, $J_{1,2}$ = 7.9 Hz, 1 H, 5-H), 4.64 (dd, $J_{1,1}$ = 9.0 Hz, $J_{1,2}$ = 7.8 Hz, 1 H, 5-H), 4.77 [m, 1 H, CH(O-)], 6.8 (m, 3 H, aromatic H). − MS (70 eV): *m*/*z* (%): 2,76 (9) [$M^+$], 208 (100) [$M^+ - C_5H_9$], 150 (71) [$C_8H_6O_3$], 135 (17) [$C_8H_7O_2$], 117 (17) [$C_8H_5O$], 104 (29) [$C_7H_4O$], 99 (21) [$C_5H_7O_2$], 69 (87) [$C_5H_9$]. − $C_{16}H_{20}O_4$ (276.4): calcd. C 69.55, H 7.29; found C 69.41, H 7.26.

*General Procedure for the Conversion of Lactones* **13** *into Amides* **18**: A 250-ml one-necked flask was charged with dimethylamine hydrochloride (20 g, 0.25 mol) and water (20 ml) and equipped with a magnetic stirrer and a reflux condenser. The latter was connected to the top of a vertical drying jar filled with KOH pellets by means of a tube. The bottom of the drying jar was connected to a 100-ml three-necked flask equipped with a septum and a drying tube. The one-necked flask was kept in a water bath and the three-necked flask was cooled to −78°C. Sodium hydroxide (20 g, 0.5 mol) was added in small portions through the reflux condenser to the solution of dimethylamine hydrochloride which was heated to 40−50°C. The dimethylamine thus liberated was collected in the 100 ml flask and finally diluted with 3 ml of abs. methanol.

A mixture of the lactone **13** (1.27 mmol) and abs. methanol (5.5 ml) was treated with the solution of dimethylamine, prepared as described above. After stirring under $N_2$ for 4 d at room temp., the solvent was removed in a rotary evaporator.

According to this procedure the following were obtained:

*(R)-4-Hydroxy-N,N-dimethyl-3-phenylbutanamide* [(*R*)-**18a**]: Prepared from **13a** (0.080 g, 0.49 mmol); yield: 0.10 g (98%), colorless oil; $[\alpha]_D^{20}$ = −14.2 (*c* = 0.7 in 95% aqueous ethanol). − $^1$H NMR (300 MHz): δ = 2.78 (m, 2 H, 2-H), 2.92 and 2.94 [2s, 3 H each, $N(CH_3)_2$], 3.41 (m, 1 H, 3-H), 3.78 (m, 3 H, 4-H and OH), 7.3 (m, 5 H , aromatic H). − $C_{12}H_{17}NO_2$ (207.3): calcd. C 69.54, H 8.27; found C 69.46, H 8.22.

*(R)-3-(3-Cyclopentyloxy-4-methoxyphenyl)-4-hydroxy-N,N-dimethylbutanamide* [(R)-**18b**]: Prepared from **13b** (0.350 g, 1.27 mmol), the crude product solidified and was recrystallized to give 0.376 g (92%) of colorless (*R*)-**18b**; m.p. 92°C; $[\alpha]_D^{20}$ = −29.8 (*c* = 1.04 in absolute ethanol). − $^1$H NMR (300 MHz): δ = 1.6 and 1.9 [2m, 8 H, $(CH_2)_4$], 2.74 (m, 2 H, 2-H), 2.95 and 2.96 [2s, 3 H each, $N(CH_3)_2$], 3.35 (m, 1 H, 3-H), 3.75 (m, 3 H, 4-H and OH), 3.82 (s, 3 H, $ArOCH_3$), 4.76 [m, 1 H, CH(O-)], 4.77 (m, 3 H, aromatic H). The $^1$H-NMR spectrum in the presence of $Eu(hfc)_3$ reveals an enantiomer excess of 87% *e.e.* − MS (70 eV); *m*/*z* (%): 321 (1.5) [$M^+$], 304 (7) − OH], 303 (35) [$M^+ - H_2O$], 235 (53) [$M^+ - C_5H_{10}O$], 164 (47) [$C_{10}H_{12}O_2$], 72 (100) [$CON(CH_3)_2$]. − $C_{18}H_{27}NO_4$ (321.4): calcd. C 67.25, H 8.47, N 4.36; found C 67.13, H 8.43, N 4.30.


[1] Reviews: [1a] B. M. Trost, *Tetrahedron* **1977**, *33*, 2615−2649. − [1b] J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, New York **1980**. − [1c] B. M. Trost, *Acc. Chem. Res.* **1980**, *13*, 385−393. − [1d] B. M. Trost, *Pure Appl. Chem*. **1981**, *53* 2357−2370. − [1e] J. Tsuji, *Pure Appl. Chem*. **1982**, *54*, 197−206. − [1f] S. A. Godleski *in Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, Oxford, **1991**, Vol. 4, p. 585−661. − [1g] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089−1122. − [1h] O. Reiser, *Angew. Chem*. **1993**, *105*, 576−578; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 547. − [1i] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395−422.

[2] B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.* **1978**, *100*, 3435−3443.

[3] [3a] T. Hayashi, A. Yamamoto, T. Hagihara, *J. Org. Chem*. **1986**, *51*, 723−727. − [3b] T. Hayashi, M. Kawatsura, Y. Uozumi, *J. Am. Chem. Soc*. **1998**, *120*, 1681−1687.

[4] J.-C. Fiaud, J.-Y. Legros, *J. Org. Chem*. **1987**, *52*, 1907−1911.

[5] [5a] B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc*. **1992**, *114*, 9327−9343. − [5b] P. Van Matt, A. Pfaltz, *Angew. Chem*. **1993**, *105*, 614−615; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 566. − [5c] J. Sprinz, G. Helmchen, *Tetrahedron Lett*. **1993**, *34*, 1769−1772. − [5d] G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett*. **1993**, *34*, 3149−3150. − [5e] G. C. Lloyd-Jones, A. Pfaltz, *Angew. Chem*. **1995**, *107*, 534−536; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 462. − [5f] G. J. Dawson, J. M. J. Williams, S. J. Coote, *Tetrahedron: Asymmetry* **1995**, *6*, 2535−2546. − [5g] H. Steinhagen, M. Reggelin, G. Helmchen, *Angew. Chem*. **1997**, *109*, 2199−2202; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2108−2110. − [5h] R. Prétôt, A. Pfaltz, *Angew. Chem*. **1998**, *110*, 337−339; *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 323−325.

[6] Partly published in a preliminary communication: M. Braun, K. Opdenbusch, C. Unger, *Synlett* **1995**, 1174−1176.

[7] [7a] H. Mahler, M. Braun, *Chem. Ber.* **1991**, *124*, 1379−1395. − [7b] M. Braun, K. Opdenbusch, *Liebigs Ann.* **1997**, 141−154.

[8] T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, J. A. Ibers, *J. Organomet. Chem*. **1974**, *65*, 253−266.

[9] B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, T. J. Dietsche, *J. Am. Chem. Soc*. **1978**, *100*, 3416−3426.

[10] [10a] T. Mukaiyama, K. Fujimoto, T. Takeda, *Chem. Lett*. **1979**, 1207−1210. − [10b] G. Helmchen, G. Nill, *Angew. Chem*. **1979**, *91*, 66−68; *Angew. Chem. Int. Ed. Engl*. **1979**, *18*, 65.

[11] [11a] T. Honda, F. Ishikawa, K. Kanai, S. Sato, D. Kato, H. Tominaga, *Heterocycles* **1996**, *42*, 109−112. − [11b] Cf. J.

Mulzer, J. Kroll (Schering AG), DE 4 032 059 1990; *Chem. Abstr.* **1992**, *117*, 90131e.
[12] R. Schmiechen, R. Horowski, D. Palenschat, G. Paschelke, H. Wachtel, W. Kehr (Schering AG), US Pat 4 193 926; DE 2 413 935 (20. 03. 1974), *Chem. Abstr.* **1976**, *84*, 30878u.
[13] Reviews on syntheses of Rolipram: J. Mulzer, *J. Prakt. Chem.* **1994**, *336*, 287−291; T. Wirth, *Syntheseplanung − aber wie?* Spektrum Akademischer Verlag, Heidelberg **1998**, p. 147−159.
[14] M. Braun, *Angew. Chem.* **1998**, *110*, 444−465; *Angew. Chem. Int. Ed.* **1998**, *37*, 430−451 and references given therein.
[15] H. G. Kuivila, *Synthesis* **1970**, 499−509; *Adv. Organomet. Chem.* **1964**, *1*, 47−87; W. P. Neumann, *Synthesis*, **1987**, 665−683; M. Pereyre, J.-P. Quintard, A. Rahm, *Tin in Organic Synthesis*, Butterworths, London **1987**, p. 35; J. O. Metzger, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. **1952**, Vol. E 19a, 1, p. 166.
[16] R. Devant, U. Mahler, M. Braun, *Chem. Ber.* **1988**, *121*, 397−406.

[O98303]