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# A Versatile Stereocontrolled Approach to Chiral Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Sequential Asymmetric Horner−Wadsworth−Emmons and Ring-Closure Reactions

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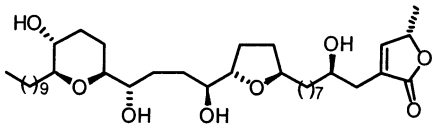
An approach to chiral tetrahydrofuran and tetrahydropyran derivatives based on the sequential use of an asymmetric Horner−Wadsworth−Emmons reaction and a cyclization step is presented. The approach is both stereochemically and structurally versatile since three different cyclization methods can be employed starting from the same HWE product: (i) palladium-catalyzed substitution, (ii) hetero-Michael addition, or (iii) epoxide opening. The asymmetric HWE reaction controls the absolute configuration of the ultimate product, whereas the relative configuration is controlled by the combined influence of the geometric selectivity in the HWE reaction and the stereochemistry of the respective cyclization method.

## Introduction

Functionalized tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives are receiving attention because of their frequent occurrence as subunits in many types of bioactive natural products, such as annonaceous acetogenins,[1] polyether antibiotics,[2] and several groups of macrolides.[3] The range of biological activities exhibited by these types of compounds is very wide, including among others antibiotic,[2] antimicrobal,[1] cytotoxic,[3,4] pesticidal,[1] antimalarial,[1] and antiviral[5] effects. For example, studies of the annonaceaous acetogenins, a class of natural products found in the tropical plant family Annonaceae, have increased considerably in recent years. Structurally, the annonaceaous acetogenins are derivatives of long-chain fatty acids containing THF and/or THP as well as butenolide moieties. Several of these compounds are potent cytotoxic agents, acting by blocking mitochondrial complex I (NADH-ubiquinone oxidoreductase) and by inhibiting plasma membrane NADH oxidase. For example, mucocin (**1**) is up to 10 000 times more selective at inhibiting A-548 (lung cancer) and PACA-2 (pancreatic cancer) cell lines compared to the known antitumor agent adriamycin.[6]




**1**

The need for appropriately functionalized building blocks, such as those shown in Chart 1, has motivated the development of many different synthetic approaches.[7] Among previously reported methods for preparing functionalized THF and THP derivatives, some of the more frequently used are acid-induced ring closure of an epoxy alcohol,[8] intramolecular hetero-Michael addition,[9] metal-catalyzed oxidative cyclization of a hydroxyalkene,[10] reduction of bicyclic ketals,[11] oxabicyclic systems,[12] or spiro compounds,[13] intramolecular Williamson-type reactions,[14] and [3 + 2] annulation of allylsilanes and aldehydes.[15]

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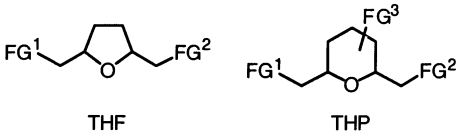
**CHART 1**

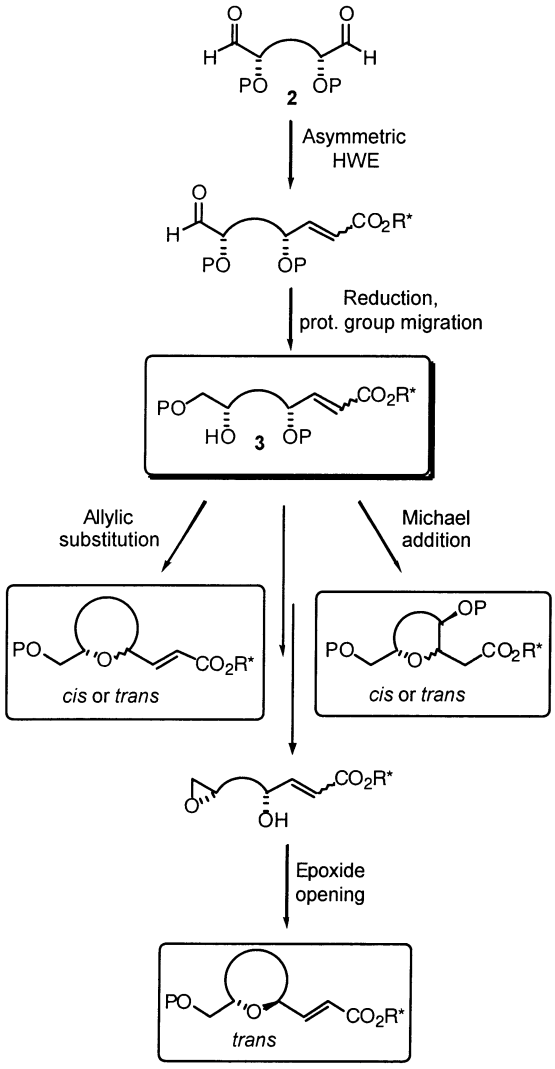



In this paper, we describe a stereochemically versatile approach to cis- and trans-substituted THF and THP derivatives of the types illustrated above (Chart 1) that is based on the sequential use of an asymmetric Horner−Wadsworth−Emmons (HWE) reaction[16] with a dialdehyde and a ring closure via either (i) an intramolecular Pd(0)-catalyzed allylic substitution,[17] (ii) a hetero-Michael addition,[9] or (iii) an intramolecular opening of a terminal epoxide (Scheme 1).[18] The fact that the use of different cyclization methods leads to different THF or THP derivatives from the same HWE product makes the overall strategy versatile.

## Results and Discussion

**Synthetic Strategies.** We have previously reported that α-oxygen-substituted *meso*-dialdehydes of type **2** can be efficiently desymmetrized by use of an asymmetric HWE reaction, giving either the (*E*)- or the (*Z*)-alkene as product with essentially full control of geometric selectivity and with good to excellent levels of asymmetric induction.[16j] The key intermediate **3**, obtained after reduction of the unreacted formyl group accompanied by protective group migration to the formed primary hydroxyl, can directly afford a THF or THP derivative via a Pd(0)-catalyzed allylic substitution or a hetero-Michael addition, in both cases with the liberated secondary hydroxyl acting as an internal nucleophile (Scheme 1). Control of the alkene geometry in **3** translates into control of the relative configuration of the ring-closed product, a fact that makes this approach attractive (Scheme 2). Generally, (*E*)-allylic substrates are known to undergo Pd(0)-catalyzed allylic substitution with O-nucleophiles with overall *retention* of configuration,[17] and **4** would thus be converted to **6**; (*Z*)-allylic compounds, on the other hand, might undergo a $\pi-\sigma-\pi$ rearrangement of the intermediate palladium complex before the nucleophilic attack takes place, resulting in overall *inversion* of configuration to give **7** from **5**.[19] In hetero-

**SCHEME 1**

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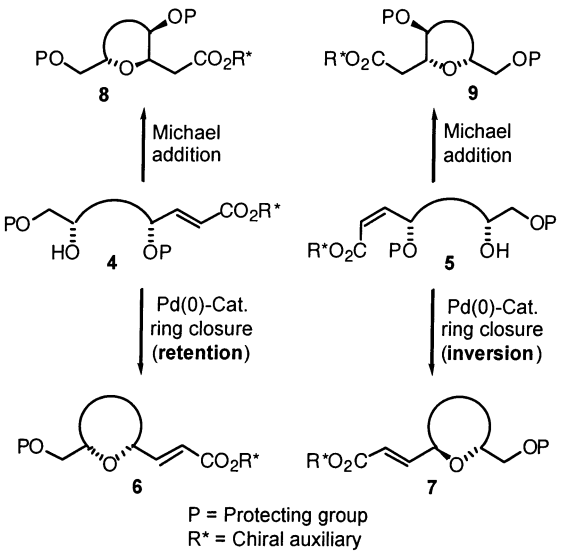
**SCHEME 2**

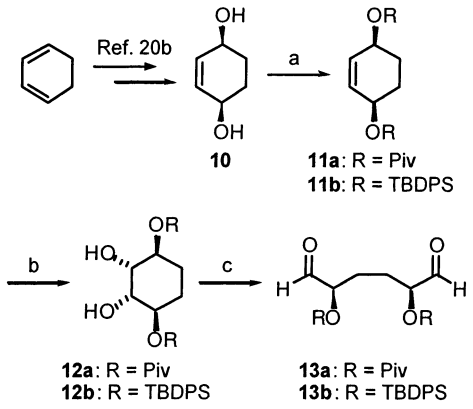



Michael additions, a (*Z*)-alkene substrate normally affords a product having the substituents vicinal to the ring oxygen in a cis relationship (e.g., **9**), both under kinetic and thermodynamic control.[9] In contrast, an (*E*)-alkene substrate can give predominantly trans product (e.g., **8**) under conditions of kinetic control, while thermodynamic control tends to favor the cis product.[9] In the case of the route proceeding via opening of a terminal epoxide, a few additional steps are needed to convert the intermediate **3** into an epoxide (Scheme 1), which subsequently is opened via an $S_N2$ reaction by the allylic alcohol to form the corresponding oxacycle.

**Choice and Preparation of Substrates.** We chose the α-oxygen-substituted *meso*-dialdehydes **13** and **27**[16j] as key substrates in this study for two reasons: from earlier work, we knew that dialdehydes of type **27** can perform well in asymmetric HWE reactions,[16j] and the expected HWE products are appropriately functionalized to allow further transformation to five- or six-membered oxacycles with the desired substitution patterns. The choice of hydroxyl protecting groups has particular importance by enabling the respective type of ring closure to occur. Pivaloyl protective groups were chosen as one alternative (in *meso*-dialdehydes **13a** and **27a**) since allylic carboxylates are known to be good precursors for $\eta^3$-allylpalladium complexes. Even though silyloxy groups are not suitable for Pd(0)-catalyzed substitutions due to their inability to function as leaving groups, their choice was motivated because they could be efficiently employed en route to hetero-Michael additions and epoxide opening reactions and they are often superior to pivalates when selective deprotection is needed. Furthermore, the ability of silyl groups to migrate from one oxygen to another is well-known.

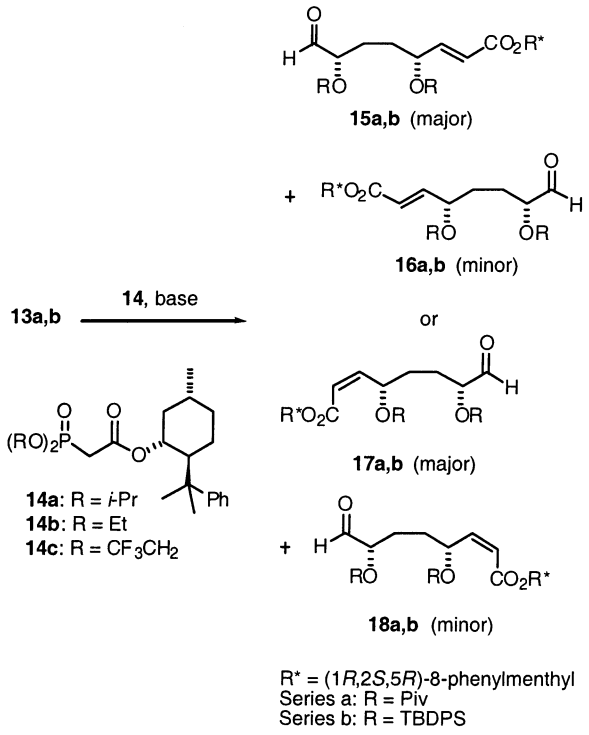
The dialdehydes **13a** and **13b** were prepared in three simple steps from the known *cis*-2-cyclohexene-1,4-diol (**10**) that, in turn, is accessible from 1,3-cyclohexadiene[20] (Scheme 3). The protected diols **11** were dihydroxylated in high yield using $RuCl_3/NaIO_4$,[21] whereas the more

**SCHEME 3**[a]




[a] Reaction conditions: (a) **11a**: PivCl, 4-DMAP, pyridine, reflux, 3 h, 59%; **11b**: TBDPSCl, imidazole, DMF, rt, 30 h, 85%; (b) **12a**: cat. $RuCl_3$, $NaIO_4$, $MeCN/H_2O$, 0 °C, 5 min, 94%; **12b**: cat. $RuCl_3$, $NaIO_4$, $MeCN/EtOAc/H_2O$, 0 °C, 60 s, 73%; (c) $H_5IO_6$, THF, rt, 70−80 min, 99% (**13a**), 96% (**13b**).

**SCHEME 4**




R* = (1*R*,2*S*,5*R*)-8-phenylmenthyl
Series a: R = Piv
Series b: R = TBDPS

conventional $OsO_4$/NMMO oxidation system gave only ca. 75% (**12a**) and 45% (**12b**) conversion, respectively, even after several days at 50 °C. The desired dialdehydes were obtained in essentially quantitative yield after oxidative cleavage with periodic acid.

**Asymmetric HWE Reactions.** For the synthesis of HWE products **15a**,**b** and **17a**,**b** (Scheme 4, Table 1), we applied the best conditions found earlier[16j] for reactions with dialdehydes **27**. The (*E*)-alkenes were obtained with good to excellent levels of asymmetric induction and in moderate yields by using diisopropyl phosphonate **14a**[16j] and the KHMDS/18-crown-6 base system (entries 1 and

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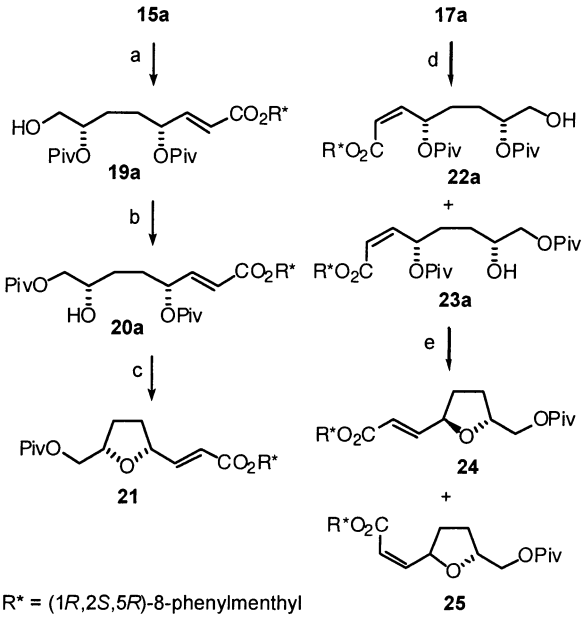
**TABLE 1. Asymmetric HWE Reactions with Dialdehydes 13**[a]

| entry | phosphonate | substrate | *T* (°C) | product | yield[b] (%) | dr[c] | yield of bisadd (%) |
|---|---|---|---|---|---|---|---|
| 1 | **14a** | **13a** | −85 | **15a** | 55 | 98:2 | 44 |
| 2 | **14c** | **13a** | −85 | **17a** | 71 | ≥98:2 | 25 |
| 3 | **14a** | **13b** | −78 | **15b** | 59[d] | 95:5 | 36 |
| 4 | **14b** | **13b** | −78 | **15b** | 69 | 80:20 | n.d.[e] |
| 5 | **14c**[f] | **13b** | −78 | **17b** | 88 | ≥98:2 | n.d. |

[a] General reaction conditions: 1.2−1.3 equiv of dialdehyde, 1.1−1.3 equiv of phosphonate, 1.0 equiv of KHMDS, 5 equiv of 18-crown-6, ca. 0.02 M in THF, 3−12 h. [b] Yield of isolated monoaddition product. [c] Ratio of **15a**,**b**/**16a**,**b** or **17a**,**b**/**18a**,**b**, respectively. The geometric selectivity was >98:2 for all entries. [d] Yield after reduction of the monoaddition product to the alcohol. [e] Not determined. [f] NaHMDS was used as base, without a crown ether.

**SCHEME 5**[a]




[a] Reaction conditions: (a) $NaBH_4$, MeOH/THF, 0 °C, 85%; (b) DMAP, EtOH, 75 °C; 63% **20a**, 27% recovered **19a** (see ref 22); (c) $Pd_2(dba)_3$·$CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 25 °C, 76%; (d) $LiBH_4$, *i*-PrOH/THF, 0 °C; 49% **23a**, 38% **22a** (see ref 22); (e) $Pd_2(dba)_3$·$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 65 °C; 78% **24**, 10% **25**.

3). When diethyl phosphonate **14b**[16j] was used instead of **14a**, the diastereoselectivity dropped significantly (entry 4). The (*Z*)-alkene products **17a** and **17b**, in turn, were obtained in high yields with essentially complete geometric and diastereoselectivities by using bis(trifluoroethyl) phosphonate **14c**[16j] (entries 2 and 5). The pivaloyl-protected dialdehyde **13a** performed best with our "standard" KHMDS/18-crown-6 base system, whereas the silyl-protected dialdehyde **13b** gave better results when NaHMDS was used as base, without a crown ether.

**Pd(0)-Catalyzed Intramolecular Allylic Substitutions.** The reduction of the remaining aldehyde functionality in HWE products **15a** and **17a**, followed by acyl group migration, afforded intermediates **20a** and **23a**, respectively (Scheme 5). Different reagent combinations can be used for the reduction/PG-migration sequence. The use of $NaBH_4$ followed by treatment with imidazole, DMAP, or $Et_3N$ afforded roughly a 2:1 mixture of the desired secondary alcohol **20a** or **23a** and the isomeric primary alcohol **19a**[22] or **22a**,[22] respectively. The use of $LiBH_4$ as reducing agent, however, afforded directly a ca. 2:1 mixture of secondary and primary alcohols as products.

For the Pd(0)-catalyzed allylic substitution, several different ligands for palladium were tested. With dppe, all starting material was recovered, and the use of triphenylphosphine afforded predominantly an undesired diene, presumably via a $\beta$-elimination pathway. Addition of bases (pyridine, triethylamine, DBU) to increase the nucleophilicity of the hydroxyl group gave, at best, only ca. 10% of the desired product. However, use of phenanthroline-type ligands afforded the desired ring-closed products in moderate to high yields. Among the tested ligands, 2,9-dimethyl-1,10-phenanthroline (neocuproine) turned out to be the best for our system. When the (*E*)-alkene **20a** was treated with Pd(0) in the presence of neocuproine, THF derivative **21** formed readily in 76% yield with clean retention of configuration at the allylic stereocenter.

The ring closure of (*Z*)-alkene **23a** needed heating to 65 °C to proceed. The rate-determining step in this reaction is presumably the initial formation of the disfavored *syn*,*anti*-$\pi$-allylpalladium complex, which rearranges to the more stable syn,syn complex via a $\pi-\sigma-\pi$ rearrangement.[19] The subsequent nucleophilic attack then gives THF derivative **24** as the main product. The product is obtained with overall inversion of configuration at the allylic stereocenter, accompanied by (*Z*)- to (*E*)-isomerization which is consistent with the suggested $\pi-\sigma-\pi$ rearrangement.

A minor product, assigned to have structure **25**, was also isolated from this reaction in ca. 10% yield, together with some dba ligand. The (*Z*)-geometry of the alkene in **25** is proven by NMR. It is known that for monosubstituted $\eta^3$-allylpalladium complexes containing neocuproine as ligand, the syn complex is destabilized relative to the anti complex due to interference between the methyl substituents on neocuproine and the syn substituents of the $\eta^3$-allyl unit.[23] As a result, the anti complex undergoes slower rearrangement when the ligand is neocuproine, which favors retention of the (*Z*)-alkene geometry in the product when a (*Z*)-alkene is used as substrate. On the basis of this precedence, it is reasonable to assume that in the reaction giving **25**, the allylic substitution has proceeded with overall retention at the allylic stereocenter via direct ring closure of the *syn*,*anti*-palladium complex to give the relative configuration of the stereocenters in the THF ring as cis; however, an unambiguous assignment has not been possible.

(22) The primary alcohols recovered after the acyl group migration could be converted to mixtures of secondary/primary alcohols again, thereby increasing the overall yield of the desired secondary alcohol.

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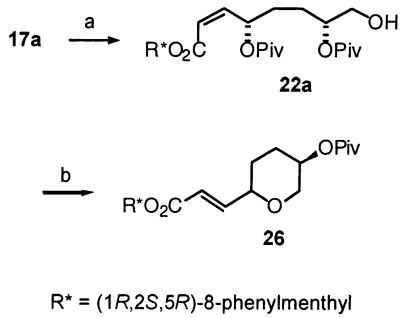
**SCHEME 6**[a]




[a] Reaction conditions: (a) $NaBH_4$, MeOH/THF, 0 °C, 88%; (b) $Pd_2(dba)_3$·$CHCl_3$ (0.05 equiv), neocuproine (0.2 equiv), THF, 65 °C, 82%.

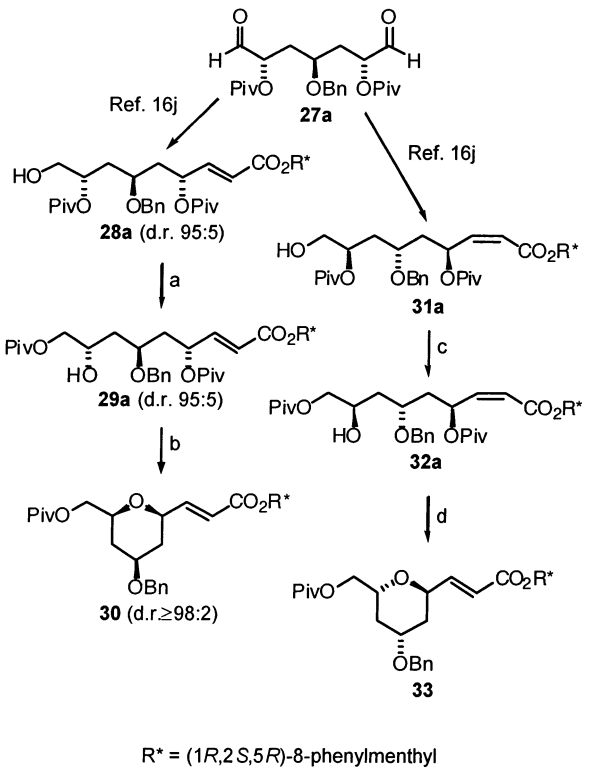
The protective group migration during the reduction of the HWE product **17a** was suppressed by using $NaBH_4$ in MeOH/THF,[24] and the primary alcohol **22a** could be isolated in high yield (Scheme 6). By subjecting **22a** to the ring-closing conditions, THP derivative **26** was obtained in good yield as a single isomer. The alkene geometry of **26** is proven by NMR to be (*E*). If it is postulated that **26** is formed via a mechanism analogous to the formation of **24** from **23a**, the relative configuration of the stereocenters in the THP ring of **26** can be tentatively assigned as cis, but this has not been unequivocally proven.

In an analogous manner to the routes to THF derivatives **21** and **24** (vide supra, Scheme 5), the products obtained from asymmetric HWE reactions with dialdehyde **27a**[16j] could be converted into THP derivatives as shown in Scheme 7.[16m] Base-induced migration of one pivaloyl group transformed **28a** and **31a** to **29a** and **32a**, respectively.[22] Subsequent palladium-catalyzed ring closure then afforded **30**[25] and **33** in diastereomerically pure form.

**Hetero-Michael Additions.** We found that HWE products **15b** and **17a**,**b** could be readily converted into trisubstituted THP's via a hetero-Michael addition (Scheme 8). The intermediates **20b** and **23a**,**b** were obtained from the HWE products by reduction of the remaining formyl group accompanied by migration of one silyl or pivaloyl protective group to the adjacent primary hydroxyl. The bulky silyl groups were more prone to migration than the pivalate esters, and the migration occurred readily even when $NaBH_4$ was used as reducing agent, affording a ca. 5:1 mixture of the corresponding secondary and primary alcohols.[22,24] When the (*E*)-alkene **20b** was treated with base (*t*-BuOK), 2,6-*trans*-THP **34** was obtained as product in excellent yield and selectivity (**34**/**35** = 97:3). The (*Z*)-alkenes **23**, in contrast, afforded exclusively 2,6-*cis*-THPs **36** as products under analogous reaction conditions.

The difference in stereoselectivity could depend on either the difference in alkene geometry or the difference in relative stereochemistry between the auxiliary and the other stereocenters (or a combination of the two). Based on earlier studies by Banwell[9a] and Martín,[9b,c] we believe that the former factor is more important than the latter. According to the mechanistic model proposed by Martin,[9b] the transition states leading from the (*E*)- and (*Z*)-alkenes to 2,6-*trans*- and 2,6-*cis*-THP derivatives, respectively, are shown in Scheme 9. The 2,6-cis product should be thermodynamically favored in both cases, implying that at least the formation of the 2,6-*trans*-alkene **34** proceeds via kinetic control. Upon longer reaction time and higher temperature, the trans/cis ratio **34**/**35** dropped significantly, supporting the suggested formation of **34** via kinetic control.

**SCHEME 7**[a]




[a] Reaction conditions: (a) imidazole, EtOH, 75 °C; 59% **29a**, 28% recovered **28a** (see footnote 22); (b) $Pd_2(dba)_3$·$CHCl_3$ (0.1 equiv), neocuproine (0.4 equiv), THF, 25 °C, 80%; (c) DMAP, EtOH, 75 °C; 48% **32a**, 42% recovered **31a** (see ref 22); (d) $Pd_2(dba)_3$·$CHCl_3$ (0.15 equiv), neocuproine (0.4 equiv), THF, 50 °C, 59%.

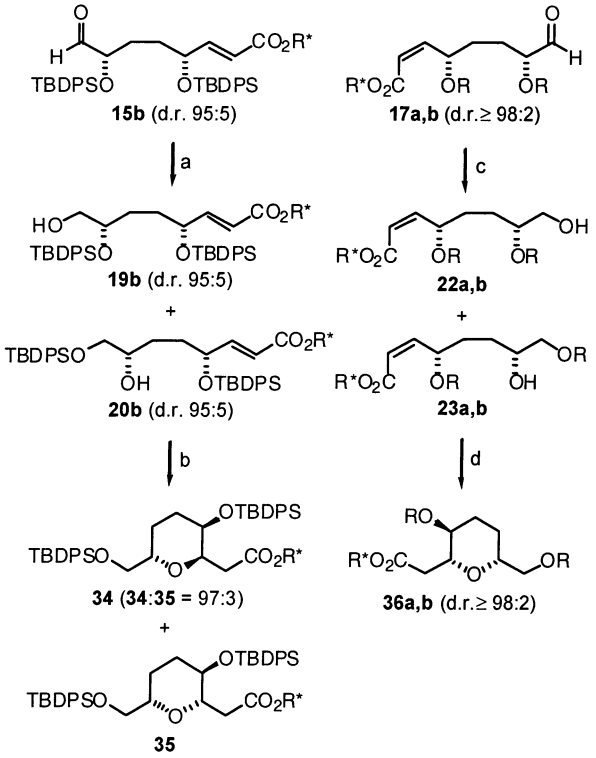
**Epoxide Opening.** We also explored the possibilities to convert the reduced HWE product **28b**[16j] into a THP derivative via intramolecular opening of a terminal epoxide by an oxygen nucleophile (Scheme 10).[16k] Normally, the opening of epoxides via an $S_N2$-type mechanism occurs with complete inversion of stereochemistry.[26] While in the case of the Pd(0)-catalyzed allylic substitution one may, by choosing a (*Z*)-alkene substrate, invert the stereochemistry at the allylic stereocenter, the epoxide opening approach instead has the allylic hydroxyl group acting as a nucleophile, and therefore the configuration is inverted at the C-8 stereocenter and retained at the allylic position. The primary hydroxyl group in triol **37**, which was obtained after cleavage of both silyl groups in **28b**, was regioselectively tosylated in 76% yield.

(24) The use of either $LiBH_4$ or $NaBH_4$ in combination with *i*-PrOH/THF resulted in much faster protective group migration during the reduction compared to when MeOH/THF was used as solvent mixture.

(25) The ring-closed product **30** was obtained in diastereomerically pure form, even though the starting material contained 5% of minor diastereomer **45** (see the Experimental Section).

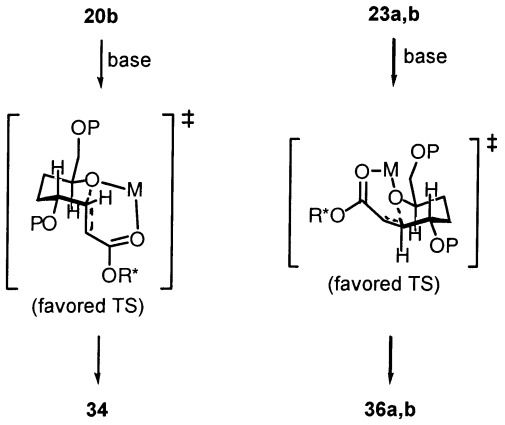
(26) For a review on epoxide openings, see: Smith, J. K. *Synthesis* **1984**, 629.

**SCHEME 8**[a]




[a] Reaction conditions: (a) $NaBH_4$, *i*-PrOH/THF, 0 °C, overall yield from **13b**: 54% **20b**, 5% **19b** (see ref 22); (b) *t*-BuOK, THF, 0 °C, 96%; (c) R = pivaloyl: see Scheme 5, step d; R = TBDPS: $NaBH_4$, *i*-PrOH/THF, 0 °C; 59% **23b**, 19% **22b** (see ref 22); (d) *t*-BuOK, $Et_2O$, rt; 95% (**36a**); 97% (**36b**).

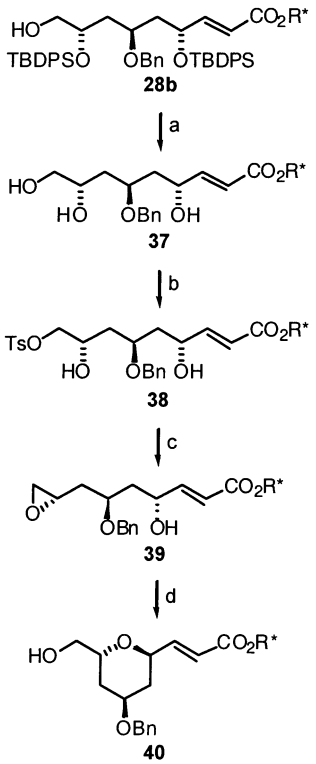
**SCHEME 9**




Subsequent treatment with base afforded the terminal epoxide **39** in 95% yield. Initial attempts to open the epoxide by activating the nucleophile with base failed, but the use of a catalytic amount of triflic acid to activate the epoxide afforded the desired 2,6-*trans*-THP derivative **40** as a single isomer in good yield.

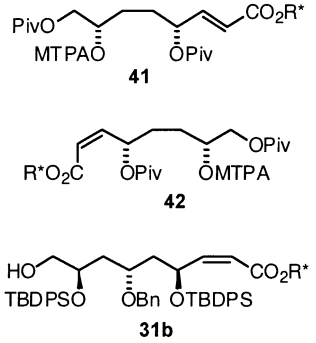
**Determination of Absolute and Relative Configurations.** The absolute configurations of the pivaloyl-protected HWE products **15a** and **17a** were assigned on the basis of $^1$H NMR analyses of both diastereomers of

**SCHEME 10**[a]




[a] Reaction conditions: (a) *n*-$Bu_4NF$, THF, rt, 80%; (b) TsCl, pyridine, 0 °C, 76%; (c) NaHMDS, THF, rt, 95%; (d) cat. $CF_3SO_3H$, MeCN, 0 °C, 89%.

**CHART 2**

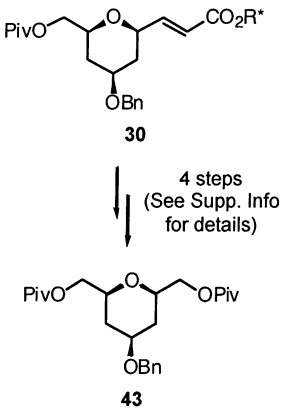



the Mosher ester derivatives **41** and **42** (Chart 2), respectively, according to the method developed by Mosher and Dale, and extended by Kakisawa et al.[27] The absolute configurations of the silyl-protected HWE products **15b** and **17b** were assigned on the basis of analogies with compounds **15a**/**17a** and **28b**/**31b** (Chart 2).[16j]

The assignments of relative configurations for the ring-closed products **21**, **24**, **33**, **36a**, and **40** are based on NOE experiments. The assignment for compound **30** is based on $^1$H and $^{13}$C NMR analysis of derivative **43** (Scheme 11), which is meso (not pseudo-$C_2$-symmetric) implying

(27) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092, and references therein. For details regarding the NMR analyses of the Mosher esters **41** and **42**, see the Supporting Information.

**SCHEME 11**




## Conclusions

that the stereochemistry of **30** is the one shown. The relative configurations of the hetero-Michael products **34** and **36b** are assigned on the basis of $^{13}C$ NMR analysis.[28]

### Conclusions

In this paper, we have demonstrated that the use of an asymmetric HWE reaction with a *meso*-dialdehyde followed by a ring-closure reaction is an efficient and versatile strategy for the synthesis of several types of substituted THF and THP derivatives possessing different relative configurations. In the asymmetric HWE reactions, either (*E*)- or (*Z*)-monoaddition products could be obtained with essentially complete geometric control by slight structural variation in the phosphoryl group of the chiral phosphonate reagent; furthermore, both (*E*)- and (*Z*)-products were obtained in good to excellent diastereoselectivities and good yields. Three different methods were employed for converting the products from the asymmetric HWE reactions into THF or THP derivatives: (i) intramolecular Pd(0)-catalyzed allylic substitution, (ii) hetero-Michael addition, or (iii) intramolecular opening of a terminal epoxide. These methods give products with different and complementary substitution patterns as well as relative configurations.

### Experimental Section

**General Methods.** Reagent and solvent purification, work-up procedures, and analyses were in general performed as described previously.[16j] If not otherwise indicated, isolated compounds were colorless oils.

***meso*-(3*R*,6*S*)-3,6-Bis(2,2-dimethylpropionyloxy)cyclohex-1-ene (11a).** To a solution of diol **10**[20] (1.01 g, 8.85 mmol, 86:14 mixture of cis and trans isomers) and 4-(dimethylamino)-pyridine (1.08 g, 8.85 mmol) in 30 mL of dry pyridine was added pivaloyl chloride (5.5 mL, 44.3 mmol). The reaction mixture was refluxed for 3 h, diluted with 1 M HCl, and extracted with EtOAc. Drying, concentration, and purification by flash chromatography (2−6% EtOAc in hexanes) afforded 1.48 g (59%) of *cis*-ester **11a** and 1.01 g (40%) of a ca. 1.4:1 mixture of cis and trans isomers. **11a**: $R_f = 0.45$ (hexanes/EtOAc 9/1); $^1H$ NMR (250 MHz) $\delta$ 5.84 (app d, $J = 1.4$ Hz, 2H), 5.20−5.13 (m, 2H), 1.94−1.68 (m, 4H), 1.18 (s, 18 H); $^{13}C$ NMR (62.9 MHz) $\delta$ 178.0, 130.2, 67.0, 38.6, 27.0, 24.8; IR 2972, 1728, 1480, 1279, 1156, 1035, 1019 cm$^{-1}$; HRMS-FAB (*m*/*z*) $[M]^+$ calcd for $C_{16}H_{26}O_4$ 282.1831, found 282.1821.

***meso*-(3*R*,6*S*)-3,6-Bis(*tert*-butyldiphenylsilyloxy)cyclohex-1-ene (11b).** To a solution of crude diol **10**[20] (2.2 g, 19.3 mmol, 86:14 mixture of cis and trans isomers) and imidazole (6.56 g, 96.5 mmol) in 190 mL of dry DMF was added TBDPSCl (13.3 g, 48.4 mmol). After the mixture was stirred for 30 h at rt, EtOAc was added, and the organic layer was washed with water, dried, filtered, and concentrated. Purification by flash chromatography (0−10% EtOAc in hexanes) afforded 9.7 g (85%) of bis-silyl ether **11b** (86:14 mixture of cis and trans isomers). This mixture could be used without further separation in the subsequent step.[29] **11b**: $R_f = 0.3$ (1.6% EtOAc in hexanes); $^1H$ NMR (250 MHz) $\delta$ 7.82−7.67 (m, 8H), 7.52−7.31 (m, 12H), 5.65 (br s, 2H), 4.14 (br t, $J = 4.8$ Hz, 2H), 2.0−1.84 (m, 2H), 1.62−1.45 (m, 2H), 1.15 (s, 18H); $^{13}C$ NMR (62.9 MHz) $\delta$ 135.7, 134.3, 131.8, 129.4, 127.4, 66.6, 28.2, 26.8, 19.1; IR 2958, 2931, 2857, 1428, 1111, 1082, 701, 506 cm$^{-1}$. Anal. Calcd for $C_{38}H_{46}O_2Si_2$: C, 77.23; H, 7.85. Found: C, 76.98; H, 7.73.

***meso*-(1*R*,2*S*,3*S*,6*R*)-3,6-Bis(2,2-dimethylpropionyloxy)-cyclohexane-1,2-diol (12a). Method a.**[21b] A solution of alkene **11a** (447 mg, 1.58 mmol) in $CH_3CN$ (26 mL) was cooled to 0 °C. A solution of $RuCl_3$ hydrate (38 mg, ca. 0.17 mmol) and $NaIO_4$ (818 mg, 3.75 mmol) in 5 mL of $H_2O$ was then added. The reaction mixture was stirred vigorously for 5 min and then quenched with 20% aq $Na_2S_2O_3$ (5 mL). The aqueous phase was separated and extracted with EtOAc. Drying, filtration, and concentration followed by flash chromatography (25% EtOAc in hexanes) afforded 473 mg (94%) of diol **12a** as a colorless oil that slowly solidified. **12a**: $R_f = 0.2$ (hexanes/EtOAc 3/1); $^1H$ NMR (250 MHz) $\delta$ 5.00 (br s, 2H), 3.84 (app dd, $J = 8.2$, 2.4 Hz, 2H), 3.20 (br s, 2H), 1.97−1.82 (m, 2H), 1.73−1.56 (m, 2H), 1.20 (s, 18H); $^{13}C$ NMR (62.9 MHz) $\delta$ 178.5, 72.0, 71.5, 38.8, 27.1, 23.7; IR 3481, 2974, 1732, 1481, 1283, 1156, 734 cm$^{-1}$. Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.85. Found: C, 61.07; H, 8.87. **Method b.** To a solution of alkene **11a** (397 mg, 1.41 mmol) and *N*-methylmorpholine *N*-oxide (165 mg, 1.41 mmol) in a mixture of THF, *t*-BuOH, and $H_2O$ (16, 8, and 4 mL, respectively) was added 540 $\mu$L of a 2.5 wt % solution of $OsO_4$ in *t*-BuOH (0.042 mmol). The reaction mixture was stirred for 60 h at 55 °C and then quenched by the addition of $Na_2S_2O_3$ (5 mL, 20% aq solution). Dilution with brine followed by extraction (EtOAc), drying, and concentration afforded 425 mg of crude product. Purification by flash chromatography (4−40% EtOAc in hexanes) afforded 65 mg (16%) of unreacted alkene **11a** and 340 mg (76%) of diol **12a** as a colorless oil that slowly solidified.

***meso*-(1*R*,2*S*,3*S*,6*R*)-3,6-Bis(*tert*-butyldiphenylsilyloxy)-cyclohexane-1,2-diol (12b). Method a.**[21a] A solution of alkene **11b** (cis/trans 86:14; 50 mg, 0.085 mmol) in a mixture of EtOAc (3 mL) and $CH_3CN$ (3 mL) was cooled to 0 °C. A solution of $RuCl_3$ hydrate (2 mg, ca. 0.009 mmol) and $NaIO_4$ (50 mg, 0.23 mmol) in 1 mL of $H_2O$ was then added to the alkene solution. The two-phase mixture was vigorously stirred for 60 s and then quenched with 20% aq $Na_2S_2O_3$ (ca. 5 mL). The aqueous phase was separated and extracted (EtOAc). Drying of the combined organic extracts, concentration, and flash chromatography (10% EtOAc in hexanes) afforded 39 mg

(28) In a separate experiment, performed at higher temperature and for a longer reaction time, a ca. 70:30 mixture of **34** and **35** was obtained as product from **20b**. In compound **34**, the carbons at C-2 and C-6 give $^{13}C$ NMR peaks at 73.8 and 68.5 ppm, respectively, whereas the corresponding carbons in the minor product **35** give peaks at 79.2 and 72.2 ppm, respectively. In 2,6-*trans*-THP derivatives the carbons at C-2 and C-6 are, on average, shifted upfield by ca. 7 ppm compared to the same carbons in the corresponding 2,6-*cis*-THP derivative; see: (a) Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; VCH Publishers: New York, 1994; pp 108−114. (b) Eliel, E. L.; Manoharan, M.; Pietrusiewicz, K. M.; Hargrave, K. D. *Org. Magn. Reson.* **1983**, *21*, 94.

(29) The cis and trans isomers could be separated by careful flash chromatography (2−8% EtOAc in hexanes).

(73%) of diol **12b**. Only one stereoisomer was detected by $^1$H and $^{13}$C NMR. **12b**: $R_f$ = 0.15 (hexanes/EtOAc 9/1); $^1$H NMR (250 MHz) $\delta$ 7.73−7.61 (m, 8H), 7.47−7.32 (m, 12H), 4.00−3.85 (m, 4H), 2.29 (br s, 2H), 1.66−1.32 (m, 4H), 1.09 (s, 18H); $^{13}$C NMR (62.9 MHz) $\delta$ 135.74, 135.65, 134.0, 133.8, 129.8, 129.7, 127.7, 127.6, 73.7, 71.9, 27.0, 26.7, 19.3; IR 3579, 2931, 2857, 1428, 1105, 701, 501 cm$^{-1}$; HRMS-FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{38}H_{48}O_4Si_2$ 625.3169, found 625.3169. **Method b.** To a solution of alkene **11b** (cis/trans 86:14; 2.32 g, 3.92 mmol) and *N*-methylmorpholine *N*-oxide (508 mg, 4.34 mmol) in 14 mL of THF were added *t*-BuOH (7 mL) and $H_2O$ (3.5 mL), followed by a solution of $OsO_4$ in *t*-BuOH (2.5 wt %, 1.52 mL, 0.118 mmol). The reaction mixture was stirred for 60 h at 45 °C and then quenched with 5 mL of 20% aq $Na_2S_2O_3$. Dilution with brine followed by extraction (EtOAc), drying, concentration, and flash chromatography (10% EtOAc in hexanes) afforded 1.12 g (46%) of diol **12b** as a single stereoisomer.

***meso*-(2*R*,5*S*)-2,5-Bis(2,2-dimethylpropionyloxy)hexanedial (13a).** To a solution of diol **12a** (127 mg, 0.402 mmol) in THF (8 mL) was added a solution of $H_5IO_6$ (91.6 mg, 0.402 mmol) in THF (8 mL) at 0 °C. After 80 min at rt, 5 mL of phosphate buffer (pH 7) and 10 mL of brine was added. The solution was extracted (EtOAc), dried, and concentrated. The residue was dissolved in $CHCl_3$ (2 mL) and filtered through a plug of cotton, giving 126 mg (99%) of **13a** as a white solid. Due to its limited stability, the dialdehyde was generally used in HWE reactions without further purification. **13a**: $^1$H NMR (200 MHz) $\delta$ 9.47 (d, $J$ = 0.7 Hz, 2H), 5.03−4.87 (m, 2H), 2.04−1.74 (m, 4H), 1.26 (s, 18H); $^{13}$C NMR (50.3 MHz) $\delta$ 197.8, 177.9, 77.1, 38.8, 27.0, 24.2; IR 3466, 2974, 1732, 1481, 1282, 1151 cm$^{-1}$.

***meso*-(2*R*,5*S*)-2,5-Bis(*tert*-butyldiphenylsilyloxy)hexanedial (13b).** To a solution of diol **12b** (210 mg, 0.335 mmol) in THF (7 mL) was added a solution of $H_5IO_6$ (84 mg, 0.368 mmol) in THF (4 mL) at 0 °C. After 70 min at rt, 10 mL of brine was added. The solution was extracted with EtOAc, dried, and concentrated to give 201 mg (96%) of **13b** as a white solid. The dialdehyde was used in HWE reactions without further purification. **13b**: $^1$H NMR (200 MHz) $\delta$ 9.49 (br d, $J$ = 1.2 Hz, 2H), 7.25−7.68 (m, 20H), 4.04−3.94 (m, 2H), 1.82−1.69 (m, 2H) 1.64−1.52 (m, 2H), 1.09 (s, 18H); $^{13}$C NMR (50.3 MHz) $\delta$ 203.2, 135.7, 132.8, 130.0, 127.8, 77.5, 27.4, 26.9, 19.3; IR 2931, 2859, 1737, 1428, 1112, 702, 505 cm$^{-1}$. Anal. Calcd for $C_{38}H_{46}O_4Si_2$: C, 73.27; H, 7.44. Found: C, 73.00; H, 7.43.

**General Procedure for the Asymmetric HWE Reactions.** To a solution of the chiral phosphonate (**14a**−**c**, 1.1 equiv) and 18-crown-6 (if applicable, 5 equiv) in dry THF (ca. 0.02 M with respect to the phosphonate) at −78 °C under argon was added 1.0 equiv of KHMDS (0.5 M in tolune) or NaHMDS (0.6 M in toluene). After 30 min, the resulting slurry was transferred via cannula to a precooled solution of the dialdehyde (**13a**,**b**) in a small volume of dry THF. The reaction mixture was stirred at the indicated temperature for 3−12 h (monitoring by TLC) and then quenched with phosphate buffer (pH 7). After dilution with brine, extractive workup (EtOAc), drying, concentration, and flash chromatography (EtOAc in hexanes) afforded the products.

**(*E*)-(4*R*,7*S*)-4,7-Bis(2,2-dimethylpropionyloxy)-8-oxooct-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (15a).** Prepared from **13a** and **14a** in 55% yield. (*E*)/(*Z*) ≥ 98:2, diastereomeric ratio **15a**/**16a** = 98:2. **15a**: $R_f$ = 0.56 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 9.47 (d, $J$ = 0.6 Hz, 1H), 7.28−7.16 (m, 4H), 7.13−7.03 (m, 1H), 6.45 (dd, $J$ = 15.7, 5.1 Hz), 5.38 (dd, $J$ = 15.7, 1.6 Hz, 1H), 5.34−5.26 (m, 1H), 4.98−4.90 (m, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 1.27 (s, 9H), 1.21 (s, 9H), 0.86 (d, $J$ = 6.5, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) $\delta$ 197.8, 177.9, 177.1, 164.9, 151.4, 143.6, 127.8, 125.3, 124.9, 122.4, 77.2, 74.6, 70.9, 50.3, 41.6, 39.6, 38.9, 38.8, 34.5, 31.2, 29.0, 27.7, 27.1, 26.5, 25.1, 24.1, 21.7; IR 2960, 2928, 1732, 1480, 1280, 1152, 733 cm$^{-1}$. Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.50; H, 8.89. **16a**: $^1$NMR (250 MHz, selected data assigned from a 98:2 mixture of diastereomers **15a**/**16a**) $\delta$ 6.16 (dd, $J$ = 16.0, 4.3 Hz, 1H).

**(*E*)-(4*R*,7*S*)-4,7-Bis(*tert*-butyldiphenylsilyloxy)-8-oxooct-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (15b).** Prepared from **13b** and **14a.** An approximately 2:1 mixture of mono- and bis-HWE condensation products was obtained. The bis-HWE byproduct was readily separated after reduction of **15b** to alcohol **19b** (vide infra). **15b**: $^1$NMR [250 MHz, assigned from a mixture of diastereomers **15b**/**16b** (95:5) and bis-HWE product] $\delta$ 9.44 (d, $J$ = 1.5 Hz, 1H), 7.65−6.98 (m, 25 H), 6.63 (dd, $J$ = 15.6, 5.3 Hz, 1H), 5.56 (dd, $J$ = 15.6, 1.5 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.4, 1H), 4.33−4.24 (m, 1H), 4.24−4.12 (m, 1H), 3.98−3.91 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 1.09 (s, 9 H), 1.06 (s, 9H), 0.89 (d, $J$ = 6.4 Hz, 3H). **16b**: $^1$NMR [250 MHz, selected data assigned from a mixture of diastereomers **15b**/**16b** (95:5) and bis-HWE product] $\delta$ 9.43 (d, $J$ = 1.5 Hz, 1H).

**(*Z*)-(4*S*,7*R*)-4,7-Bis(2,2-dimethylpropionyloxy)-8-oxooct-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (17a).** Prepared from **13a** and **14c** in 71% yield. (*Z*)/(*E*) ≥ 98:2, dr **17a**/**18a** ≥ 98:2. **17a**: $R_f$ = 0.56 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 9.50 (d, $J$ = 0.6 Hz, 1H), 7.27−7.17 (m, 4H), 7.14−7.04 (m, 1H), 6.07 (app br q, $J$ = 6 Hz, 1H), 5.81 (dd, $J$ = 11.5, 7.6 Hz, 1H), 5.02 (dd, $J$ = 11.5, 1.4 Hz, 1H), 5.03−4.95 (m, 1H), 4.79 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 1.28 (s, 9H), 1.17 (s, 9H), 0.86 (d, $J$ = 6.5, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 197.9, 178.0, 177.5, 164.4, 151.6, 146.4, 127.8, 125.2, 124.9, 121.2, 77.5, 74.2, 70.9, 50.3, 41.6, 39.5, 38.7, 38.6, 34.4, 31.2, 29.4, 27.9, 27.1, 27.0, 26.4, 24.6, 24.5, 21.7; IR 2962, 2928, 1714, 1480, 1202, 1152 cm$^{-1}$; $[\alpha]_{546}$ +4.0 (*c* 8.3, $CHCl_3$). Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.55; H, 8.83. Found: C, 71.55; H, 8.79.

**(*Z*)-(4*S*,7*R*)-4,7-Bis(*tert*-butyldiphenylsilyloxy)-8-oxooct-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (17b).** Prepared from **13b** and **14c** in 88% yield. (*Z*)/(*E*) ≥ 98:2; diastereomeric ratio **17b**/**18b** ≥ 98:2. **17b**: $R_f$ = 0.55 (hexanes/EtOAc 85/15); $^1$H NMR (250 MHz, selected data) $\delta$ 9.50 (d, $J$ = 1.54 Hz, 1H), 7.68−7.04 (m, 25H), 5.94 (dd, $J$ = 11.6, 8.0 Hz, 1H), 5.39−5.28 (m, 1H), 4.81 (dd, $J$ = 11.6, 1.3 Hz, 1H), 4.63 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.09−4.0 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.13 (s, 9H), 1.03 (s, 9H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz, some singals overlap) $\delta$ 203.3, 164.4, 151.5, 151.4, 135.8, 135.7, 134.0, 133.8, 133.1, 133.0, 129.9, 129.6, 129.5, 127.9, 127.8, 127.7, 127.5, 127.4, 125.3, 125.0, 118.5, 78.0, 73.8, 69.4, 50.4, 41.6, 39.6, 34.5, 32.1, 31.2, 28.0, 27.2, 27.0, 26.6, 25.5, 21.8, 19.4, 19.2; IR 2958, 2858, 1713, 1428, 1198, 1112, 700 cm$^{-1}$; $[\alpha]_{546}$ +14.8 (*c* 2.83, $CHCl_3$).

**General Procedure for Reduction of the HWE Products.** To a solution of aldehyde in a 1:1 mixture of MeOH/THF or *i*-PrOH/THF (0.015 M with respect to the aldehyde) was added $NaBH_4$ or $LiBH_4$ (3−5 equiv) at 0 °C. After being stirred at 0 °C until the reaction was finished (monitoring by TLC), the reaction mixture was diluted with brine, extracted (EtOAc), dried, filtered, concentrated, and purified by flash chromatography (EtOAc in hexanes) to afford the product.

**General Procedure for Protective Group Migration.** To a solution of the primary alcohol in EtOH (ca. 0.03 M with respect to alcohol) was added an amine (4-DMAP, $Et_3N$, or imidazole). After the mixture was refluxed for ca. 15 h, the ethanol was evaporated, and the mixture of secondary and primary alcohols was separated by flash chromatography.[22]

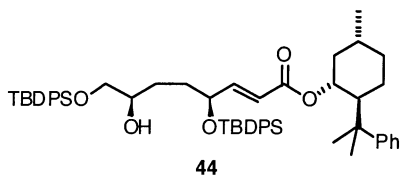
**(*E*)-(4*R*,7*S*)-4,7-Bis(2,2-dimethylpropionyloxy)-8-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (19a).** Prepared from **15a** in 85% yield. **19a**:[30] $R_f$ = 0.28 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.27−7.17 (m, 4H), 7.14−7.04 (m, 1H), 6.49 (dd, $J$ = 15.7, 5.1 Hz, 1H), 5.39 (dd, $J$ = 15.7, 1.6 Hz, 1H), 5.34−5.25 (m, 1H), 4.91−4.80 (m, 1H), 4.85 (ddd [app td],

(30) A single diastereomer could be detected by $^1$H NMR.

$J$ = 10.6, 4.3 Hz, 1H), 3.69 (dd, $J$ = 11.9, 4.0 Hz, 1H), 3.61 (dd, $J$ = 11.9, 5.8 Hz, 1H), 1.21 (s, 18H), 0.86 (d, $J$ = 6.5, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) $\delta$ 178.6, 177.2, 165.1, 151.3, 144.1, 127.9, 125.4, 125.0, 122.1, 74.65, 74.56, 71.3, 64.7, 50.4, 41.6, 39.7, 38.9, 34.5, 31.2, 29.5, 27.4, 27.1, 26.6, 25.9, 25.5, 21.7; IR 3504, 2958, 2928, 1731, 1480, 1281, 1157, 1032 cm$^{-1}$.

**(*E*)-(4*R*,7*S*)-4,8-Bis(2,2-dimethylpropionyloxy)-7-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester 20a.** Prepared from **19a**; 52% of secondary alcohol **20a** and 38% of a 1:2.5 mixture of secondary and primary alcohols (**20a** and **19a**, respectively) was obtained.[22] **20a**:[30] $R_f$ = 0.33 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.28−7.18 (m, 4H), 7.15−7.06 (m, 1H), 6.52 (dd, $J$ = 15.7, 5.1 Hz, 1H), 5.41 (dd, $J$ = 15.7, 1.6 Hz, 1H), 5.37−5.28 (m, 1H), 4.86 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 4.12 (dd, $J$ = 11.3, 3.4 Hz, 1H), 3.97 (dd, $J$ = 11.3, 6.8 Hz, 1H), 3.90−3.78 (m, 1H), 1.22 (s, 9H), 1.21 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 178.7, 177.4, 165.1, 151.4, 144.4, 127.9, 125.4, 125.4, 122.1, 74.7, 71.7, 69.8, 68.4, 50.4, 41.7, 39.7, 38.9, 34.5, 31.3, 29.9, 29.7, 28.6, 27.4, 27.19, 27.15, 26.6, 25.5, 21.8; IR 3522, 2958, 2926, 1732, 1282, 1155 cm$^{-1}$; $[\alpha]_{546}$ +9.8 (*c* 1.5, $CHCl_3$).

**(*E*)-(4*R*,7*S*)-4,8-Bis(*tert*-butyldiphenylsilyloxy)-7-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (20b) and (*E*)-(4*R*,7*S*)-4,7-Bis(*tert*-butyldiphenylsilyloxy)-8-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (19b).** The reduction of the crude **15b** (mixture with the corresponding bis-HWE product, vide supra) with $NaBH_4$ according to the general procedure afforded three fractions: (a) (*E*,*E*)-bis-HWE product (39%); (b) **20b** (diastereomeric ratio **20b**/**44**[31] = 95:5, 52%); and (c) a 78:22 mixture of **19b** and **20b** (dr 95:5) (7%).[22] **20b**: $^1$H NMR [250 MHz, selected data assigned from a mixture (95:5) of diastereomers **20b** and **44**] $\delta$ 7.70−7.57 (m, 8H) and 7.50−7.05 (m, 17H), 6.68 (dd, $J$ = 15.6, 5.2 Hz, 1H), 5.62 (dd, $J$ = 15.6, 1.5 Hz, 1H), 4.86 (ddd [app td], $J$ = 10.6, 4.3 Hz, 1H), 4.35−4.25 (m, 1H), 3.53 (dd, $J$ = 10.7, 3.2 Hz, 1H) and 3.38 (dd, $J$ = 9.8, 8.0 Hz, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.08 (s, 18H), 0.89 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 165.6, 150.9, 149.3, 135.8, 135.5, 129.8, 129.7, 127.9, 127.8, 127.6, 127.5, 125.5, 125.2, 121.1, 74.6, 72.1, 71.8, 67.9, 50.6, 41.8, 40.1, 34.5, 32.5, 31.3, 28.1, 27.3, 27.0, 26.8, 25.3, 21.8, 19.3, 19.1; IR 2957, 2930, 2858, 1712, 1428,1112, 735, 701, 505 cm$^{-1}$; $[\alpha]_{546}$ +18.5 (*c* 1.24, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.32; H, 8.45. **44**: $^1$NMR [250 MHz, selected data assigned from a mixture (95:5) of diastereomers **20b** and **44**] $\delta$ 6.32 (dd, $J$ = 15.6, 5.2 Hz, 1H), 5.46 (dd, $J$ = 15.6, 1.5 Hz, 1H). **19b**: $^1$NMR (250 MHz, selected data) $\delta$ 6.61 (dd, $J$ = 15.6, 5.3 Hz, 1H), 5.53 (dd, $J$ = 15.6, 1.4 Hz, 1H).




**44**

**(*E*)-3-[(2*R*,5*S*)-5-(2,2-Dimethylpropionyloxymethyl)tetrahydrofuran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (21).** Neocuproine hemihydrate (1.3 mg, 0.006 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (1.5 mg, 0.0015 mmol) were dissolved in 1 mL of THF, and the solution was added via syringe to a solution of alkene **20a** (8.5 mg, 0.015 mmol) in 2 mL of THF. After the mixture was stirred for 45 min at rt, 1 mL of 2% aq HCl was added. Filtration through a plug of $MgSO_4$, concentration, and flash chromatograpy of the residue (7.5% EtOAc in hexanes) afforded 5.3 mg (76%) of **21**. **21**:[30] $R_f$ = 0.48 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.29−7.20 (m, 4H), 7.17−7.07 (m, 1H), 6.59 (dd, $J$ = 15.6, 4.8 Hz, 1H), 5.52 (dd, $J$ = 15.6, 1.6 Hz, 1H), 4.84 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.44 (app br qd, $J$ = 4.9, 1.6 Hz, 1H), 4.26−4.16 (m, 1H), 4.14 (dd, $J$ = 11.5, 4.0 Hz, 1H), 4.06 (dd, $J$ = 11.4, 5.2 Hz, 1H), 1.30 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) $\delta$ 178.5, 165.7, 151.5, 147.3, 127.9, 125.4, 125.0, 120.9, 78.2, 77.2, 74.4, 66.0, 50.5, 41.7, 39.7, 38.8, 34.6, 31.3, 27.6, 27.2, 26.6, 25.7, 21.8; IR 2955, 1714, 1278, 1162 cm$^{-1}$; $[\alpha]_{546}$ −8.4 (*c* 0.5, $CHCl_3$); HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{29}H_{42}O_5$ 470.3032, found 470.3050.

**(*Z*)-(4*S*,7*R*)-4,8-Bis(2,2-dimethylpropionyloxy)-7-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23a) and (*Z*)-(4*S*,7*R*)-4,7-Bis(2,2-dimethylpropionyloxy)-8-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (22a).** The reduction of **17a** with $LiBH_4$, according to the general procedure, afforded 49% of secondary alcohol **23a** and 38% of primary alcohol **22a**,[22] which were readily separated by flash chromatography (12% EtOAc in hexanes). **23a**:[30] $R_f$ = 0.4 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.28−7.18 (m, 4H), 7.16−7.06 (m, 1H), 6.15−6.03 (m, 1H), 5.83 (dd, $J$ = 11.5, 7.7 Hz, 1H), 5.05 (dd, $J$ = 11.5, 1.3 Hz, 1H), 4.79 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.15 (dd, $J$ = 11.2, 3.3 Hz, 1H), 4.01 (dd, $J$ = 11.2, 6.6 Hz, 1H), 3.97−3.86 (m, 1H), 1.23 (s, 9H), 1.17 (s, 9H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 178.7, 177.7, 164.5, 151.6, 146.9, 127.9, 125.4, 124.9, 121.0, 74.4, 71.4, 70.0, 68.4, 50.4, 47.9, 41.6, 39.6, 38.9, 34.5, 31.3, 30.0, 29.0, 27.8, 27.2, 27.1, 26.5, 25.0, 21.1; IR 3528, 2960, 1732, 1715, 1283, 1202, 1155, 702 cm$^{-1}$; $[\alpha]_{546}$ −1.9 (*c* 1.6, $CHCl_3$). **22a**:[30] $R_f$ = 0.27 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.25−7.17 (m, 4H), 7.14−7.05 (m, 1H), 6.10−6.00 (m, 1H), 5.81 (dd, $J$ = 11.5, 7.6 Hz, 1H), 5.01 (dd, $J$ = 11.5, 1.3 Hz, 1H), 4.97−4.87 (m, 1H), 4.79 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.71 (br dd, $J$ = 11.9, 3.2 Hz, 1H), 3.64 (br dd, $J$ = 11.9, 6.5 Hz, 1H), 1.23 (s, 9H), 1.17 (s, 9H), 0.85 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 178.9, 177.7, 164.4, 151.6, 146.9, 127.8, 125.3, 124.9, 120.9, 74.8, 74.2, 71.2, 64.8, 50.4, 41.6, 39.6, 38.9, 38.6, 34.4, 31.2, 29.7, 27.8, 27.1, 27.0, 26.45, 26.36, 24.8, 21.7; IR 3524, 2971, 1728, 1283, 1201, 1156 cm$^{-1}$.

**(*Z*)-(4*S*,7*R*)-4,8-Bis(*tert*-butyldiphenylsilyloxy)-7-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (23b) and (*Z*)-(4*S*,7*R*)-4,7-Bis(*tert*-butyldiphenylsilyloxy)-8-hydroxyocta-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (22b).** The reduction of **17b** with $NaBH_4$, according to the general procedure, afforded 59% of alcohol **23b** and 19% of alcohol **22b**.[22] **23b**:[30] $^1$H NMR (250 MHz, selected data) $\delta$ 7.70−7.53 (m, 8H), 7.47−7.04 (m, 17H), 5.97 (dd, $J$ = 11.7, 8.0 Hz, 1H), 5.41−5.29 (m, 1H), 4.80 (dd, $J$ = 11.7, 1.2 Hz, 1H), 4.58 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.73−3.64 (m, 1H), 3.61 (dd, $J$ = 9.8, 3.5 Hz, 1H), 3.45 (dd, $J$ = 9.8, 7.3 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 1.07 (s, 9H), 1.03 (s, 9H), 0.88 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals overlap) $\delta$ 164.4, 151.7, 151.4, 135.8, 135.5, 134.1, 133.9, 133.2, 129.8, 129.6, 129.5, 127.8, 127.76, 127.5, 127.4, 125.3, 125.0, 118.3, 74.0, 72.1, 69.6, 68.0, 50.4, 41.6, 39.6, 34.5, 33.5, 31.2, 27.9, 27.2, 27.0, 26.9, 26.6, 25.5, 21.8, 19.2; IR 2956, 2930, 2858, 1713, 1428, 1198, 1112, 700 cm$^{-1}$; $[\alpha]_{546}$ +26.3 (*c* 1.9, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.09; H, 8.26. **22b**:[30] $^1$H NMR (250 MHz, selected data) $\delta$ 7.72−7.03 (m, 25H), 5.84 (dd, $J$ = 11.7, 8.0 Hz, 1H), 5.33−5.22 (m, 1H), 4.76 (dd, $J$ = 11.7, 1.3 Hz, 1H), 4.60 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 3.84−3.72 (m, 1H), 3.44 (br s, 1H), 3.43 (d, $J$ = 2.2 Hz, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.07 (s, 9H), 0.99 (s, 9H), 0.87 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 164.4, 151.8, 151.4, 135.9, 135.8, 135.7, 135.65, 135.5, 134.8, 134.0, 133.9, 133.6, 129.7, 129.54, 129.47, 127.9, 127.74, 127.66, 127.5, 127.4, 125.4, 125.0, 118.2, 74.2, 73.8, 69.6, 65.8,

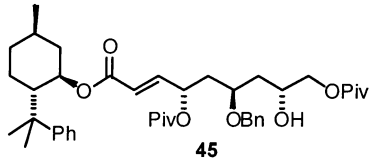
(31) Compound **44** originates from **16b**, the minor diastereomer formed in the reaction between **13b** and **14a**.

50.4, 41.7, 39.7, 34.5, 32.8, 31.2, 28.5, 27.2, 27.1, 27.0, 26.6, 25.6, 21.8, 19.4, 19.2; IR 2955, 2945, 2855, 1715, 1195, 1115, 702 $cm^{-1}$.

**(*E*)-3-[(2*R*,5*R*)-5-(2,2-Dimethylpropionyloxymethyl)-tetrahydrofuran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (24).** Neocuproine hemihydrate (3.4 mg, 0.0155 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.0039 mmol) were dissolved in 1 mL of THF and the solution added via syringe to a solution of alkene **23a** (22.1 mg, 0.0387 mmol) in 2 mL of THF. After the mixture was heated to 65 °C for 1.5 h, an additional portion of 2 mg (0.002 mmol) of $Pd_2(dba)_3$·$CHCl_3$ was added. After another 1.5 h at 65 °C, the THF was evaporated, and the crude product was purified by flash chromatography (5% EtOAc in hexanes) to give 14.3 mg (78%) of **24**. In addition, ca. 10% of a compound tentatively assigned as the ring-closed (*Z*)-product **25** was isolated in a separate fraction, together with some dba ligand. **24**:[30] $R_f$ = 0.53 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.30−7.20 (m, 4H), 7.17−7.05 (m, 1H), 6.52 (dd, *J* = 15.6, 4.9 Hz, 1H), 5.49 (dd, *J* = 17.6, 1.6 Hz, 1H), 4.85 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.52 (app br qd, *J* = 6.7, 1.6 Hz, 1H), 4.26 (br quintet, *J* = 5.8 Hz, 1H), 4.12 (dd, *J* = 11.5, 4.2 Hz, 1H), 4.05 (dd, *J* = 11.5, 5.4 Hz, 1H), 1.22 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 1H); $^{13}$C NMR (62.9 MHz, some signals in aliphatic region overlap) $\delta$ 178.4, 165.6, 151.5, 147.2, 127.9, 125.4, 125.0, 120.8, 78.0, 76.8, 74.5, 50.5, 41.6, 39.7, 38.8, 34.5, 31.5, 31.3, 29.7, 27.9, 27.3, 27.2, 26.6, 25.6; IR 2958, 2924, 1732, 1283, 1156, 700 $cm^{-1}$; $[\alpha]_{546}$ +17.4 (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.76; H, 9.19. **25**:[30] $R_f$ = 0.56 (hexanes/EtOAc 3/1); $^1$H NMR (500 MHz, selected data) $\delta$ 7.27−7.22 (m, 4H), 7.14−7.10 (m, 1H), 6.13 (dd, *J* = 11.5 Hz, 7 Hz, 1H), 5.23 (app br q, *J* = 7 Hz, 1H), 5.07 (dd, *J* = 11.5 Hz, 1.5 Hz, 1H), 4.77 (app td, *J* = 11, 4.5 Hz, 1H), 4.21−4.15 (m, 1H), 4.12 (dd, *J* = 11.5, 4 Hz, 1H), 4.07 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.38−2.30 (m, 1H), 1.30 (s, 3H), 1.22 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 178.4, 170.0, 151.4, 150.3, 127.9, 125.4, 125.0, 119.9, 77.2, 76.8, 72.3, 66.2, 50.1, 41.7, 39.7, 38.8, 34.5,31.8, 31.3, 28.2, 27.6, 27.2, 26.6, 25.3, 21.8; IR 2955, 2925, 1730, 1710, 1170, 1090 $cm^{-1}$.

**(*E*)-3-[(2*R*,5*R*)-5-(2,2-Dimethylpropionyloxy)tetrahydropyran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (26).** To a solution of primary alcohol **22a** (35.5 mg, 0.062 mmol) in 3 mL of THF were added $Pd_2(dba)_3$·$CHCl_3$ (6 mg, 0.0058 mmol) and neocuproine hemihydrate (5 mg, 0.023). The reaction mixture was refluxed for 2 h, cooled to rt, and concentrated. Purification by flash chromatography (8% EtOAc in hexanes) afforded 24 mg (82%) of **26** as a white crystalline compound. **26**:[30] $R_f$ = 0.53 (hexanes/EtOAc 3/1); $^1$H (500 MHz, selected data) $\delta$ 7.29−7.22 (m, 4H), 7.12−7.08 (m, 1H), 6.55 (dd, *J* = 15.8, 4.4 Hz, 1H), 5.52 (dd, *J* = 15.8, 1.6 Hz, 1H), 4.86 (td, *J* = 10.7, 4.3 Hz, 1H), 4.77 (br s, 1H), 4.01 (br dt, *J* = 12.7, 1.85 Hz, 1H), 3.89 (br d quintet, *J* = 10.7, 2 Hz, 1H), 3.61 (dd, *J* = 12.7, 1.3 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 9H), 1.22 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 178.0, 165.7, 151.4, 146.5, 127.9, 125.4, 124.9, 121.0, 75.5, 74.4, 69.2, 66.4, 50.5, 41.7, 39.8, 38.9, 34.5, 31.3, 27.19, 27.16, 27.13, 26.7, 26.1, 25.8, 21.8; IR 2945, 1720, 1440, 1285, 1185, 700 $cm^{-1}$; $[\alpha]_{546}$ +24.0 (*c* 1.67, $CHCl_3$). Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.93; H, 8.90.

**(*E*)-(4*R*,6*R*,8*S*)-6-Benzyloxy-4,9-bis(2,2-dimethylpropionyloxy)-8-hydroxynon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (29a).** Prepared from **28a**[16j] according to the general procedure; 59% of secondary alcohol **29a** (diastereomeric ratio **29a**/**45**[32] = 95:5) and 28% of starting material **28a**[22] ($R_f$ = 0.21, hexanes/EtOAc 3/1) were obtained. **29a**: $R_f$ = 0.35 (hexanes/EtOAc 3/1); $^1$H NMR [250 MHz, selected data assigned from a mixture (95:5) of diastereomers **29a** and **45**] $\delta$ 7.40−7.18 (m, 9H), 7.13−7.03 (m, 1H), 6.52 (dd, *J* = 15.8, 5.2 Hz, 1H), 5.58−5.47 (m, 1H), 5.42 (dd, *J* = 15.6, 1.5 Hz, 1H), 4.85 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.17−3.93 (m, 3H), 3.83−3.68 (m, 1H), 1.23 (s, 9H), 1.22 (s, 9H), 0.86 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aliphatic region overlap) $\delta$ 178.5, 177.1, 165.1, 151.4, 144.8, 137.5, 128.6, 128.2, 128.0, 127.9, 125.4, 125.0, 121.8, 74.6, 73.2, 72.5, 69.1, 68.4, 66.9, 50.4, 41.6, 39.7, 39.4, 38.8, 37.0, 34.5, 31.2, 27.2, 26.6, 25.6, 21.8; IR 3508, 2960, 2930, 1731, 1281, 1153, 700 $cm^{-1}$; $[\alpha]_{546}$ +9.2 (*c* 3.7, $CHCl_3$).




**45**

**(*E*)-3-[(2*R*,4*R*,6*S*)-4-Benzyloxy-6-(2,2-dimethylpropionyloxymethyl)tetrahydropyran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (30).** Neocuproine hemihydrate (0.9 mg, 0.0042 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (1.1 mg, 0.001 mmol) were dissolved in 1 mL of dry THF, and the solution was added via syringe to a solution of alkene **29a** (7.2 mg, 0.0104 mmol; dr **29a**/**45** = 95:5) in 1.5 mL of THF. After the mixture was stirred for 50 min at room temperature, the THF was evaporated and the residue was purified by flash chromatograpy (7.5% EtOAc in hexanes) to give 4.9 mg (80%) of **30** as a colorless oil that slowly solidified. **30**:[30] $R_f$ = 0.52 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.38−7.21 (m, 9H), 7.16−7.06 (m, 1H), 6.52 (dd, *J* = 15.7, 4.1 Hz, 1H), 5.54 (dd, *J* = 15.7, 1.8 Hz, 1H), 4.85 (ddd [app td], *J* = 10.7, 4.3 Hz, 1H), 4.60 (app s, 2H), 4.16 (dd, *J* = 11.5, 5.8 Hz, 1H), 4.10 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.88 (dddd, *J* = 11.8, 4.0, 2.0, 2.0 Hz, 1H), 3.69−3.55 (m, 2H), 1.21 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (62.9 MHz) $\delta$ 178.4, 165.6, 151.4, 145.7, 138.2, 128.5, 127.9, 127.7, 127.5, 125.4, 125.0, 120.9, 74.5, 74.0, 73.6, 69.8, 66.4, 50.5, 41.6, 39.7, 38.8, 37.0, 34.5, 34.2, 31.2, 27.7, 27.1, 26.6, 25.8, 25.1, 21.8; IR 2951, 2922, 1726, 1710, 1283, 1176, 700 $cm^{-1}$; $[\alpha]_{546}$ +5.5 (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{37}H_{49}O_6$: C, 75.35; H, 8.37. Found: C, 75.02; H, 8.75.

**(*Z*)-(4*S*,6*S*,8*R*)-6-Benzyloxy-4,9-bis(2,2-dimethylpropionyloxy)-8-hydroxynon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (32a).** Prepared from **31a**[16j] according to the general procedure; 48% of secondary alcohol **32a** and 42% of starting material **31a**[22] ($R_f$ = 0.27, hexanes/EtOAc 3/1) were obtained. **32a**:[30] $R_f$ = 0.47 (hexanes/EtOAc 3/1); $^1$H NMR (500 MHz, selected data) $\delta$ 7.48−7.19 (m, 9H), 7.15−7.07 (m, 1H), 6.26−6.16 (m, 1H), 5.85 (dd, *J* = 11.6, 7.6 Hz, 1H), 5.04 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.81 (td, *J* = 10.7, 4.3 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7, 1H), 4.14−4.00 (m, 3H), 3.87−3.80 (m, 1H), 0.86 (d, *J* = 6.4 Hz, 3H); $^{13}$C (125 MHz, some signals overlap) $\delta$ 178.7, 177.5, 164.6, 151.7, 146.4, 133.3, 128.4, 128.3, 127.93, 127.89, 127.7, 125.4, 125.0, 121.2, 74.7, 74.5, 73.3, 71.6, 69.1, 65.7, 50.4, 41.5, 39.6, 38.7, 38.6, 37.9, 34.6, 31.4, 27.8, 27.2, 27.0, 26.6 24.9, 21.8; IR 3506, 2965, 1725, 1280, 1160, 700 $cm^{-1}$.

**(*E*)-3-[(2*R*,4*S*,6*R*)-4-Benzyloxy-6-(2,2-dimethylpropionyloxymethyl)tetrahydropyran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (33).** To a solution of **32a** (50 mg, 0.072 mmol) in 5 mL of THF were added neocuproine hemihydrate (6 mg, 0.028 mmol) and $Pd_2(dba)_3$·$CHCl_3$ (7.5 mg, 0.007 mmol) at 50 °C. After the mixture was stirred for 30 min at 50 °C, an additional portion of 4 mg of $Pd_2(dba)_3$·$CHCl_3$ was added. After being stirred for another 30 min at 50 °C, the reaction mixture was concentrated and purified by flash chromatography (10% EtOAc in hexanes) to give 25 mg (59%) of **33**. **33**:[30] $R_f$ = 0.61 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.41−7.06 (m, 10H), 6.54 (dd, *J* = 16.0, 3.4 Hz, 1H), 5.51 (dd, *J* = 16.0, 2.3 Hz, 1H),

(32) Compound **45** originates from the minor (*E*)-diastereomer formed in the asymmetric HWE reaction with **27a**.

4.87 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 4.66 (app td, $J$ = 7.9, 2.3 Hz, 1H), 4.57 (d, $J$ = 11.2 Hz, 1H), 4.53 (d, $J$ = 11.8 Hz, 1H), 4.23 (dd, $J$ = 11.6, 7.1 Hz, 1H), 4.09 (dd, $J$ = 11.6, 3.7 Hz, 1H), 3.82 (app ddd, $J$ = 13.4, 6.8, 3.3 Hz, 1H), 3.82 (app ddd, $J$ = 13.9, 9.2, 4.2 Hz, 1H), 1.23 (s, 9H), 0.87 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aliphatic region overlap) $\delta$ 178.3, 165.2, 151.3, 146.7, 138.3, 128.5, 127.9, 127.7, 127.5, 125.5, 125.0, 122.7, 74.6, 70.9, 70.4, 70.1, 69.1, 66.1, 50.6, 41.8, 39.8, 38.8, 34.7, 34.6, 33.4, 31.3, 27.2, 26.7, 25.9, 21.8; IR 2955, 2927, 1713, 1283, 1162, 1094, 700 cm$^{-1}$; $[\alpha]_{546}$ −35.7 ($c$ 0.8, $CHCl_3$). HRMS-FAB ($m/z$) $[M + H]^+$ calcd for $C_{37}H_{48}O_6$ 589.3529, found 589.3526.

**[(2*R*,3*R*,6*S*)-3-*tert*-Butyldiphenylsilyloxy-6-(*tert*-butyldiphenylsilyloxymethyl)tetrahydropyran-2-yl]acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (34).** To a solution of alkene **20b** (24 mg, 0.027 mmol; dr **20b**/**44** = 95:5) in 3 mL of THF was added *t*-BuOK (5 mg, 0.04 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then quenched with 1 mL of phosphate buffer (pH 7). Extractive workup followed by flash chromatography (3% EtOAc in hexanes) afforded 23 mg (96%) of **34**. According to NMR analysis, the product contained ca. 3% of a minor isomer, tentatively assigned as the 2,6-*cis*-THP derivative **35**.[28,33] **34**: $R_f$ = 0.48 (hexanes/EtOAc 9/1); $^1$H (500 MHz, selected data) $\delta$ 7.72−7.53 (m, 8H), 7.47−7.27 (m, 16H), 7.20−7.15 (m, 1H), 4.77 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.22−4.15 (m, 1H), 3.81 (ddd, $J$ = 10, 4.5, 4.5 Hz, 1H), 3.55 (dd, $J$ = 9.5, 4.2 Hz, 1H), 3.46−3.40 (m, 1H), 3.29 (dd, $J$ = 9.3, 7.5 Hz, 1H), 2.27 (dd, $J$ = 14.5, 3 Hz, 1H), 2.16 (dd, $J$ = 14.5, 11.5 Hz, 1H), 1.98 (br t, $J$ = 9.7 Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 1.07 (s, 9H), 1.02 (s, 9H), 0.70 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 171.7, 151.9, 135.74, 135.68, 135.6, 135.5, 129.8, 129.7, 129.6, 127.9, 127.7, 127.62, 127.57, 125.5, 124.9, 74.3, 73.8, 69.2, 68.5, 66.5, 50.4, 41.7, 39.7, 34.5, 31.2, 31.1, 28.2, 27.1, 26.96, 26.88, 26.8, 24.8, 26.5, 21.6, 19.3, 19.2; IR 2930, 2857, 1728, 1428, 1112, 700, 504 cm$^{-1}$; $[\alpha]_{546}$ +24.7 ($c$ 1.4, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.08; H, 8.31. **35**: $^1$H (500 MHz, selected data assigned from a ca. 70:30 mixture of **34** and **35**) $\delta$ 3.65 (dd, $J$ = 10, 4.5 Hz, 1H), 2.70 (dd, $J$ = 14.5, 2.6 Hz, 1H); $^{13}$C (125 MHz, selected data assigned from a ca. 70:30 mixture of **34** and **35**) $\delta$ 171.2, 151.2, 77.2, 74.7, 72.2, 66.4, 50.6, 41.6, 39.9, 34.6.

**[(2*R*,3*S*,6*R*)-3-(2,2-Dimethylpropionyloxy)-6-(2,2-dimethylpropionyloxymethyl)tetrahydropyran-2-yl]acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl Ester (36a).** To a solution of alkene **23a** (52 mg, 0.091 mmol) in 2 mL of dry ether was added *t*-BuOK (10 mg). The reaction mixture was stirred for 10 min at rt and then quenched with 0.5 mL of phosphate buffer (pH 7). Extractive workup (EtOAc/brine), drying, and evaporation of solvents afforded 54 mg (ca. 95% pure based on $^1$H NMR, crude yield 99%) of tetrahydropyran **36a**. An analytically pure sample was obtained in 95% yield after purification by flash chromatography (5% EtOAc in hexanes). **36a**:[30] $R_f$ = 0.72 (hexanes/EtOAc 3/1); $^1$H NMR (250 MHz, selected data) $\delta$ 7.30−7.19 (m, 4H), 7.14−7.06 (m, 1H), 4.82 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.36 (ddd [app br td], $J$ = 9.8, 4.6 Hz, 1H), 4.00 (dd, $J$ = 11.4, 5.0 Hz, 1H), 3.93 (dd, $J$ = 11.4, 5.8 Hz, 1H), 3.74 (ddd [app dt], $J$ = 9.9, 2.6 Hz, 1H), 3.62−3.51 (m, 1H), 1.20 (s, 9H), 1.18 (s, 9 H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals overlap) $\delta$ 178.2, 177.5, 170.4, 151.3, 127.8, 125.4, 125.1, 76.1, 75.1, 74.6, 70.8, 66.0, 50.2, 41.8, 39.7, 38.7, 37.6, 34.5, 31.3, 29.7, 28.5, 27.2, 27.1, 26.6, 25.7, 21.8; IR 2956, 2926, 2870, 1731, 1284, 1153 cm$^{-1}$; $[\alpha]_{546}$ +30.4 ($c$ 3.7, $CHCl_3$); HRMS-FAB ($m/z$) $[M + H]^+$ calcd for $C_{34}H_{52}O_7$ 573.3791, found 573.3794.

**[(2*R*,3*S*,6*R*)-3-*tert*-Butyldiphenylsilyloxy-6-*tert*-butyldiphenylsilyloxymethyltetrahydropyran-2-yl]acetic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (36b).** To a solution of **23b** (212 mg, 0.24 mmol) in 10 mL of dry ether was added *t*-BuOK (40 mg, 0.356 mmol). The reaction mixture was stirred for 30 min at rt and then quenched with 2 mL of phosphate buffer (pH 7). Extractive workup, followed by flash chromatography (3% EtOAc in hexanes), afforded 206 mg (97%) of **36b**. **36b**:[30] $R_f$ = 0.48 (hexanes/EtOAc 85/15); $^1$H NMR (500 MHz, selected data) $\delta$ 7.71−7.68 (m, 4H), 7.60−7.57 (m, 4H), 7.48−7.20 (m, 17H), 7.13−7.10 (m, 1H), 4.83 (ddd [app td], $J$ = 10.7, 4.4 Hz, 1H), 3.70 (ddd [app td], $J$ = 10.1, 2 Hz, 1H), 3.61 (dd, $J$ = 10, 4.5 Hz, 1H), 3.46−3.39 (m, 1H), 3.36−3.27 (m, 2H), 2.68 (dd, $J$ = 15, 2 Hz, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H), 0.97 (s, 9H), 0.67 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals overlap) $\delta$ 171.4, 151.2, 135.9, 135.8, 135.51, 135.45, 134.2, 133.5, 129.8, 129.7, 129.5, 127.8, 127.7, 127.6, 125.5, 125.1, 79.3, 77.6, 77.1, 74.5, 72.1, 66.3, 50.3, 41.7, 39.9, 38.7, 34.5, 32.7, 31.2, 28.0, 27.0, 26.8, 26.1, 21.6, 19.3, 19.2; IR 2956, 2931, 2857, 1725, 1427, 1111, 700 cm$^{-1}$; $[\alpha]_{546}$ +19.3 ($c$ 1.1, $CHCl_3$). Anal. Calcd for $C_{56}H_{72}O_5Si_2$: C, 76.32; H, 8.23. Found: C, 76.27; H, 8.49.

**(*E*)-(4*R*,6*R*,8*S*)-6-Benzyloxy-4,8,9-trihydroxynon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl Ester (37).** To a solution of bis-silyl ether **28b**[16j] (diastereomeric ratio ≥ 98:2; 131.7 mg, 0.13 mmol) in 7 mL of dry THF was added 525 $\mu$L (0.53 mmol) of $Bu_4NF$ solution (1 M in THF). After being stirred for 2 h at room temperature, the reaction mixture was diluted with 10 mL of aq saturated $NH_4Cl$, extracted with $CH_2Cl_2$ (3 × 20 mL), dried, filtered through a plug of cotton, and concentrated. Purification by flash chromatography (3% MeOH in $CH_2Cl_2$) yielded 55 mg (80%) of triol **37**. **37**:[30] $R_f$ = 0.31 ($CH_2Cl_2$/MeOH 19/1); $^1$H NMR (200 MHz, selected data) $\delta$ 7.42−7.18 (m, 9H), 7.16−7.04 (m, 1H), 6.58 (dd, $J$ = 15.6, 4.4 Hz, 1H), 5.53 (dd, $J$ = 15.6, 1.7 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.63 (d, $J$ = 11.2 Hz, 1H), 4.56 (d, $J$ = 11.2 Hz, 1H), 4.48−4.35 (m, 1H), 4.08−3.88 (m, 2H), 3.64 (dd, $J$ = 11.1, 3.1 Hz, 1H), 3.44 (dd, $J$ = 11.1, 6.7 Hz, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (50.3 MHz) $\delta$ 165.7, 151.5, 149.2, 137.6, 128.6, 128.2, 128.1, 127.9, 125.4, 124.9, 120.6, 74.5, 74.2, 71.9, 69.0, 68.1, 66.9, 50.4, 41.7, 39.8, 39.7, 36.5, 34.5, 31.2, 27.2, 26.6, 25.7, 21.8, 20.1; IR 3384, 2952, 1709, 1274, 1092, 700 cm$^{-1}$; HRMS-FAB ($m/z$) $[M^+]$ calcd for $C_{32}H_{44}O_6$ 524.3138, found 524.3156.

**(*E*)-(4*R*,6*R*,8*S*)-6-Benzyloxy-4,8-dihydroxy-9-(toluene-4-sulfonyloxy)non-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (38).** To a solution of triol **37** (51 mg, 0.097 mmol) in 200 $\mu$L of pyridine was added via syringe TsCl (27 mg, 0.141 mmol) dissolved in 200 $\mu$L of pyridine. After 2 h at 0 °C, an additional 18.5 mg of TsCl in 100 $\mu$L of pyridine was added. After being stirred for an additional 2 h at 0 °C, the reaction mixture was diluted with brine, extracted with $CH_2Cl_2$ (1 × 10 mL) and ether (2 × 10 mL), dried, filtered through a plug of cotton, and concentrated to give 99 mg of pale yellow oil. Flash chromatography (0.5% MeOH in $CH_2Cl_2$) yielded 50.1 mg (76%) of **38**. **38**:[30] $R_f$ = 0.18 (2% MeOH in $CH_2Cl_2$); $^1$H NMR (250 MHz, selected data) $\delta$ 7.83−7.75 (m, 2H), 7.41−7.19 (m, 11H), 7.14−7.03 (m, 1H), 6.54 (dd, $J$ = 15.6, 4.5 Hz, 1H), 5.51 (dd, $J$ = 15.6, 1.7 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.56 (s, 2 H), 4.38 (app qd, $J$ = 4.1, 1.6 Hz, 1H), 4.13−4.01 (m, 2H), 4.01 (dd, $J$ = 10.0, 3.7 Hz, 1H), 3.91 (dd, $J$ = 10.0, 6.4 Hz, 1H), 2.44 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aromatic region overlap) $\delta$ 165.6, 151.6, 148.9, 145.1, 137.5, 132.6, 129.9, 128.6, 128.2, 127.9, 125.4, 124.9, 120.7, 74.5, 73.8, 72.2, 68.0, 66.5, 50.5, 41.7, 39.74, 39.70, 36.6, 34.5, 31.3, 27.4, 26.6, 25.6, 21.8, 21.6; IR 3474, 2951, 2924, 1708, 1176, 700 cm$^{-1}$; HRMS-FAB ($m/z$) $[M + H]^+$ calcd for $C_{39}H_{50}O_8S$ 679.3305, found 679.3275.

**(*E*)-(4*R*,6*R*,8*S*)-6-Benzyloxy-4-hydroxy-8,9-oxonon-2-enoic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (39).** To a solution of tosylate **38** (63 mg,

(33) We cannot exclude the possibility that the product contains trace amounts of the 2,6-*trans*-THP product resulting from ring closure of compound **44**; we have only been able to detect product isomers **34** and **35**, however.

0.092 mmol) in 6 mL of dry THF under Ar was added dropwise NaHMDS solution (0.585 M in toluene, 190 $\mu$L, 0.111 mmol). After the mixture was stirred for 10 min at room temperature, 0.5 mL of water was added. Filtration through a layer of $MgSO_4$ and silica gel followed by evaporation gave 44 mg (95%) of **39**. No further purification was needed. **39**:[30] $R_f$ = 0.28 (hexanes/EtOAc 7/3); $^1$H NMR (250 MHz, selected data) $\delta$ 7.42−7.20 (m, 9H), 7.16−7.06 (m, 1H), 6.61 (dd, $J$ = 15.6, 4.3 Hz, 1H), 5.56 (dd, $J$ = 15.6, 1.8 Hz, 1H), 4.86 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.66 (d, $J$ = 11.2 Hz, 1H), 4.53 (d, $J$ = 11.2 Hz, 1H), 4.53−4.41 (m, 1H), 3.94 (app ddd, $J$ = 13.2, 6.4, 4.0 Hz, 1H), 3.07−2.98 (m, 1H), 2.82 (dd, $J$ = 4.9, 4.1 Hz, 1H), 2.74 (br d, $J$ = 3.2 Hz, 1H), 2.52 (dd, $J$ = 5, 2.7 Hz, 1H), 1.31 (s, 3H), 1.23 (s, 3 H), 0.87 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (62.9 MHz, some signals in the aromatic region overlap) $\delta$ 165.4, 151.3, 149.0, 137.5, 128.4, 127.8, 127.7, 125.3, 124.7, 120.5, 74.6, 74.2, 71.7, 67.9, 50.3, 49.1, 47.1, 41.5, 39.8, 39.6, 37.0, 34.4, 31.1, 26.9, 26.5, 25.7, 21.6; IR 3468, 2953, 2923, 1710, 1273, 1092, 700 cm$^{-1}$; HRMS-FAB ($m/z$) [M + H]$^+$ calcd for $C_{32}H_{42}O_5$ 507.3110, found 507.3102.

**(*E*)-3-[(2*R*,4*R*,6*R*)-4-Benzyloxy-6-hydroxymethyltetrahydropyran-2-yl]acrylic Acid (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Ester (40).** To a solution of epoxide **39** (7.4 mg, 0.0146 mmol) in 3 mL of acetonitrile was added a catalytic amount of triflic acid (0.5% solution in $CH_2Cl_2$, 40 $\mu$L) under argon at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and then quenched by addition of 50 $\mu$L of $Et_3N$. The reaction mixture was warmed to rt, diluted with water (8 mL), and extracted with EtOAc (3 × 10 mL); the combined extracts were dried, filtered through a plug of cotton, and concentrated. Purification by flash chromatograpy (20% EtOAc in hexanes) afforded 6.6 mg (89%) of tetrahydropyran **40**. **40**:[30] $R_f$ = 0.18 (hexanes/EtOAc 7/3); $^1$H NMR (250 MHz, selected data) $\delta$ 7.39−7.19 (m, 9H), 7.16−7.06 (m, 1H), 6.83 (dd, $J$ = 15.8, 4.7 Hz, 1H), 5.43 (dd, $J$ = 15.8, 1.9 Hz, 1H), 4.85 (ddd [app td], $J$ = 10.7, 4.3 Hz, 1H), 4.55 (d, $J$ = 11.8 Hz, 1H), 4.47 (d, $J$ = 11.8 Hz, 1H), 4.40 (br qd, $J$ = 5.0, 1.7 Hz, 1H), 4.21−4.09 (m, 1H), 3.87−3.76 (m, 1H), 3.64 (dd, $J$ = 11.5, 7.5 Hz, 1H), 3.56 (dd, $J$ = 11.5, 3.9 Hz, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 0.86 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (50.3 MHz, some signals in the aromatic region overlap) $\delta$ 165.5, 151.6, 147.1, 138.3, 128.4, 127.9, 127.6, 127.4, 125.5, 124.9, 120.9, 74.4, 70.6, 70.1, 69.7, 69.4, 64.1, 50.5, 41.7, 39.7, 34.6, 31.4, 31.3, 29.7, 27.3, 26.6, 25.6, 21.8; IR 3453, 2954, 2924, 1710, 1271, 1175, 1094, 700 cm$^{-1}$; HRMS-FAB ($m/z$) [M + H]$^+$ calcd for $C_{32}H_{42}O_5$ 507.3110, found 507.3112.

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**Supporting Information Available:** NMR data for compounds **41** and **42**, details concerning the preparation of compound **43** (including analytical data), general NMR data for the 8-phenylmenthyl unit, NOE spectra for compounds **21**, **24**, **33**, **36a**, and **40**, and copies of $^1$H NMR spectra for compounds **11a**, **12b**, **13a**, **17b**, **19a**, **20a**, **21**, **22a**,**b**, **23a**, **25**, **29a**, **32a**, **33**, **35**, **36a**, and **37**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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