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Articles

Synthesis and Structure−Activity Relationships of New 1,3-Disubstituted Cyclohexanes as Structurally Rigid Leukotriene B_4 Receptor Antagonists

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A series of 1-hydroxy-3-[3-hydroxy-7-phenyl-1-hepten-1-yl] cyclohexane acetic acid derivatives was designed based on postulated active conformation of leukotriene B_4 (LTB_4) and evaluated as human cell surface LTB_4 receptor (BLTR) antagonists. Binding was determined through [^{3}H]LTB_4 displacement from human neutrophils and receptor antagonistic assays by in vitro measurements of inhibition of leukocyte chemotaxis induced by LTB_4. On the basis of these assays, a structure−affinity relationship was investigated. Optimization of the acid chain length and ω-substitution of a phenyl group on the lipophilic tail were shown to be critical for binding activity. These modifications led to the discovery of compounds with submicromolar potency and selective BLTR antagonism. The most potent compound **3b**α (IC_{50} = 250 nM) was found to significantly inhibit oedema formation in a topical model of phorbolester-induced inflammation. Substantial improvement of in vitro potency was achieved by modification of the carboxylic acid function leading to the identification of the *N*,*N*-dimethylamide series. Compound **5b**α, free of agonist activity, displayed higher potency in receptor binding with an IC_{50} of 40 nM. These results support the hypothesis that the spatial relationship between the carboxylic acid and allylic hydroxyl functions is crucial for high binding affinity with BLTR.

Introduction

Among the products of the 5-lipoxygenase-catalyzed peroxidation of arachidonic acid (AA), leukotriene B_4 (LTB_4, Figure 1A) has been claimed to be the mediator of a wide variety of human inflammatory diseases.[1] LTB_4 can stimulate neutrophil chemotaxis at submicromolar concentrations,[2a] being equipotent in vitro to other major chemokines including interleukin-8 (IL-8), platelet activating factor (PAF), and *formyl*-Met-Leu-Phe (fMLP). In addition, LTB_4 production is upregulated by many other inflammatory mediators.

Other pathophysiological responses of LTB_4 include promotion of polymorphonuclear leukocyte (PMNs) aggregation and adherence to the vascular endothelium,[2b] stimulation of the release of lysosomal enzymes and superoxide radicals by PMNs,[2c] as well as an increase in vascular permeability.[2d] The involvement of LTB_4 in human inflammatory diseases is also supported by elevated concentrations of this mediator in psoriatic lesional skin,[3a,b] colonic mucosa associated with inflammatory bowel diseases[3c] (ulcerative colitis and Crohn disease), synovial fluid of patients with active rheumatoid arthritis,[3d−f] gouty effusions,[3g] sputum of cystic

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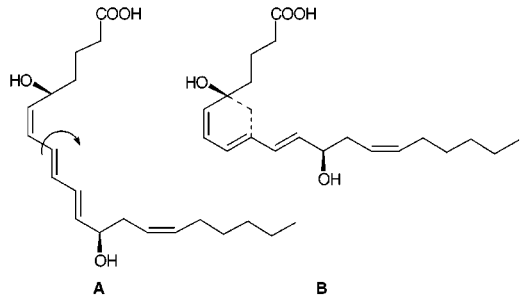


Figure 1. Possible conformers of LTB_4.

fibrosis[3h,i] and aggravation of patients suffering from chronic bronchitis,[3j] asthma,[3k] or adult respiratory distress syndrome[3l]. More recently, it has been reported that LTB_4 can activate the nuclear receptor PPARα, raising the possibility that it may be involved in feedback regulation of lipid metabolism.[4]

LTB_4 is produced by mast cells, PMNs, monocytes, alveolar macrophages, and keratinocytes. Its pharmacological effects are mediated through interaction with specific cell surface receptors on inflammatory cells.[5] These LTB_4 receptor (BLTR) sites are widely distributed and have been characterized on PMNs, monocytes, U-937 cells, lymphocytes, mast cells, smooth muscle cells, and endothelial cells, as well as on various tissues such as spleen, lung, heart, brain, small intestine, uterus, and kidney.[1c] An LTB_4 receptor gene has recently been cloned and encodes a protein of 352 amino acids predicted to have seven membrane spanning domains.[6] The G proteins associated vary with the type of cell expressing the LTB_4 receptor, allowing diversity in responses. The BLTR exists in interconvertible high (K_d, 0.1−5 nM) and low (K_d, 15−500 nM) affinity states.[7] Activation causes a rise in intracellular Ca^{2+} and inositol-triphosphate concentrations and a fall in adenylcyclase activity.

Since major proinflammatory activity of LTB_4 involves a receptor-mediated induction of the aggregation and adhesion of inflammatory cells, potent and orally active BLTR antagonists should be of benefit in the treatment of chronic neutrophil-mediated disorders. For this reason, research concerning the identification of selective BLTR antagonists has received considerable attention in the last 10 years.

The lack of direct information concerning the active conformation of LTB_4 in its receptor site, as well as the high flexibility of the molecule[8] in its free state, has complicated the selection for representative conformations mimicking the receptor-bound conformation. However, a very popular strategy has initially focused on the conformational restriction of the native ligand and replacement of its unstable triene unit with a variety of aromatic rings: benzene,[9a−9c] pyridine,[9d−9g] quinoline,[9g] thiophene,[9h] furan,[9h] or dibenzofuran.[9i] These rigid and stable analogues were shown to display good to excellent affinity for BLTR but their activity was either purely agonist[9a,d,g] or selectively antagonist for the low BLTR affinity state that is associated with degranulation.[9b,c,f]

Since then, extensive structure−activity relationship (SAR) studies have led to the identification of new generations of BLTR antagonists that did not share any obvious chemical similarity with the native ligand but displayed high affinity for BLTR binding sites and

Chart 1

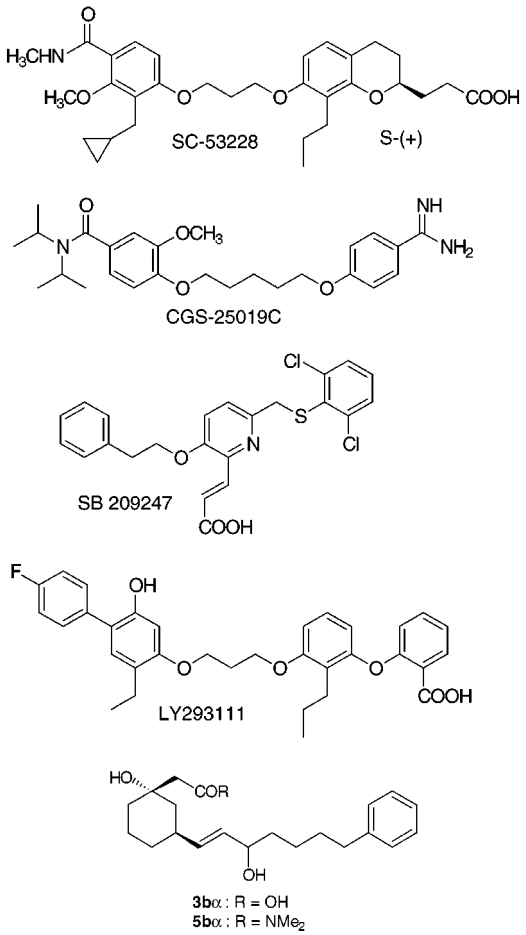


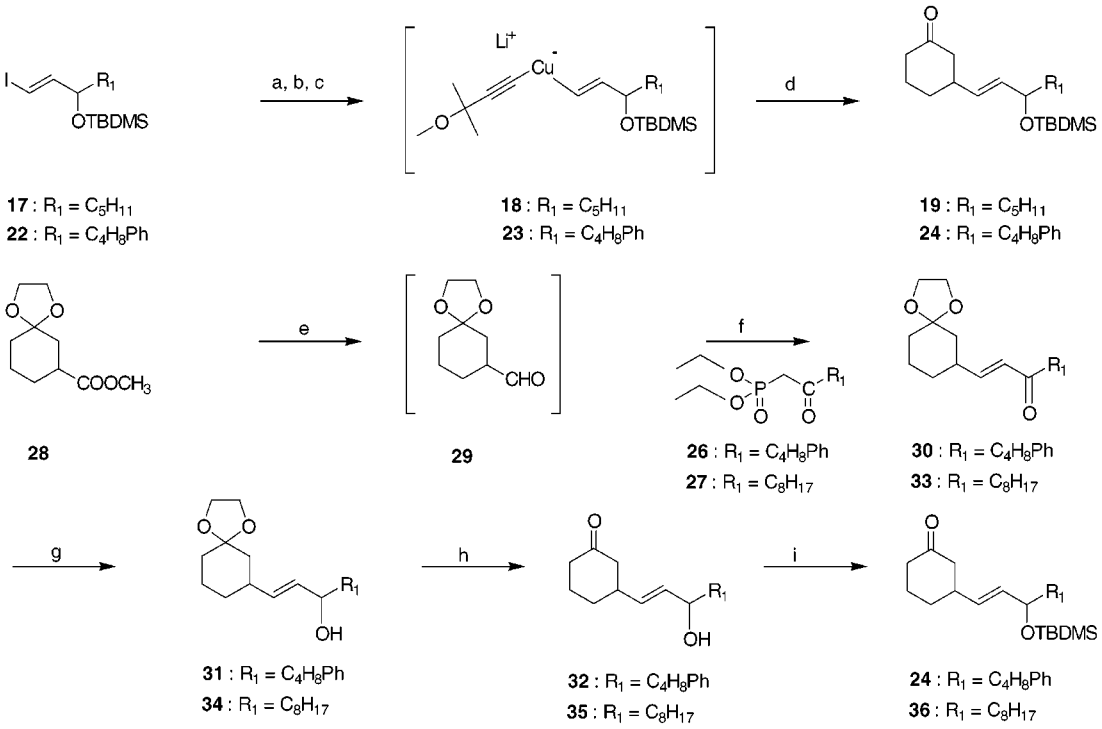
Figure 2. Structure of novel 1,3-disubstituted cyclohexane LTB4 antagonists.

potent antagonist activity in functional assays.[10a,b] Among them SC-53228,[10c] LY293111,[10d−f] SB 209247,[10g] and CGS-25019C[10a] (Chart 1) were shown to be active in animal or human models of inflammation.[10h] Some of these orally active LTBR antagonists are currently in clinical trials.

As part of our contribution toward the development of new BLTR antagonists, we investigated the possibility of replacing the triene moiety instead of an aromatic ring by a cyclohexylene moiety, using one of the energetically allowed conformations of LTB_4 as a template (Figure 1). We selected the structure B (*S*-cis geometry of the conjugated diene Δ_{6-7} and Δ_{8-9} and methylene bridge joining C5−C9). This template also mimics a collapsed conformation, as previously predicted on a theoretical basis[8a] as being the most energetically probable for a LTB_4−calcium complex. It could be the favored structure interacting with BLTR.

With this in mind, we designed the substituted cyclohexane compounds **1**−**16** as mimics of the targeted collapsed conformation of LTB_4. This strategy led to the identification of a novel series of 1,3-disubstituted cyclohexane compounds (Figure 2) exhibiting high affinity for the receptor and competitive antagonist activity both in functional assays and in acute models of inflammation. We must point out here the structurally different 1,2-disubstituted cyclohexane compounds presented by Schering Company[10i] without biological data.

Scheme 1[a]



[a] Reagents: (a) *n*-BuLi, diethyl ether, −78 °C; (b) 3-methoxy-3-methyl-but-1-yne, *n*-BuLi, diethyl ether, −78 °C; (c) CuBr, Me_2S, −20 °C; (d) 2-cyclohexen-1-one, THF, −78 °C, 88% from **17**, 75% from **22**; (e) DIBAL-H, toluene, −78 °C; (f) **26** or **27**, HNA, THF, −40 °C, 86% from **26**, 90% from **27**; (g) $NaBH_4$, $CeCl_3$, methanol, rt, 99% from **30**, 92% from **33**; (h) SiO_2, H_2SO_4, CH_2Cl_2, rt, 77%; (i) TBDMSCl, DBU, CH_2Cl_2, rt 94% from **32**, 89% from **35**.

We report here the synthesis and SAR study that led to the development of this novel series of LTB_4 antagonists.

Chemistry

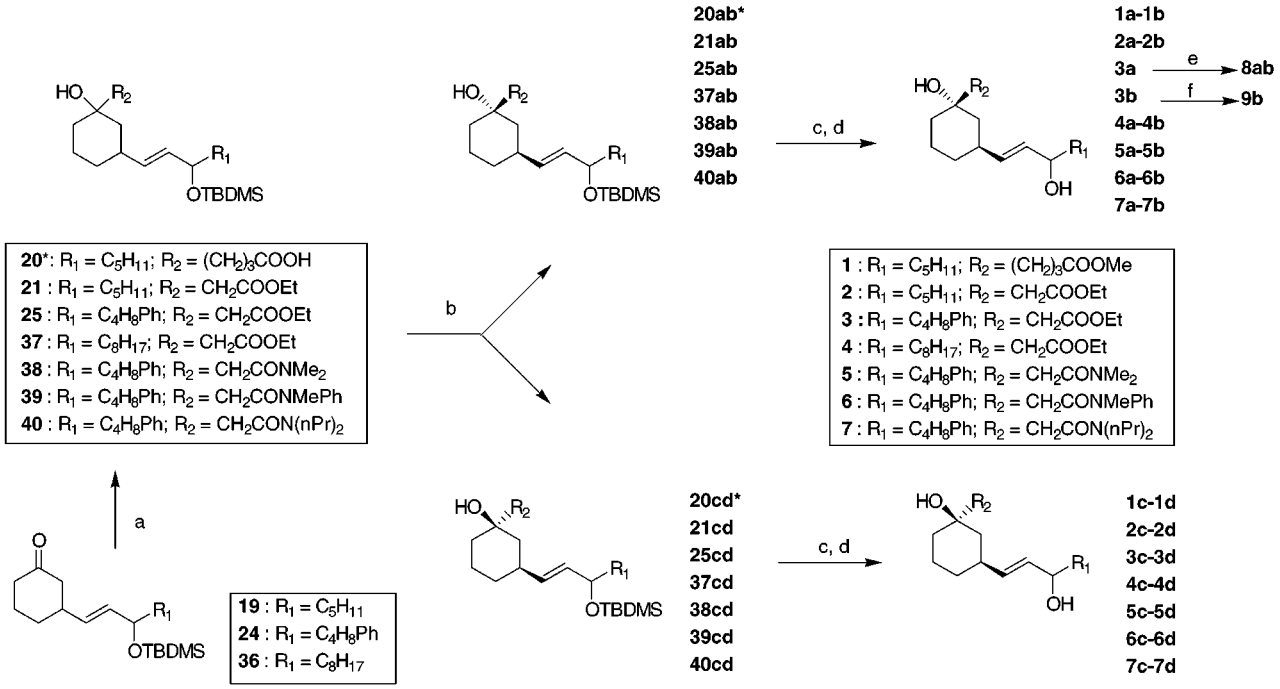
Two original synthetic pathways were developed to prepare our 1,3-disubstituted cyclohexanes. All compounds **1**−**16** were synthesized according to the procedures outlined in Schemes 1−4. The two general routes to 1,3-disubstituted cyclohexanes are exemplified for compounds **1**−**9** in Schemes 1 and 2, while the preparation of analogues **10**−**16** is illustrated in Schemes 3 and 4 and resulted from slight modifications of the former procedures.

In our initial synthesis of target compounds **1**−**3**, the lipophilic side chain was introduced on the cyclohexane ring via the coupling of the mixed homocuprates,[11a] **18** and **23**, with 2-cyclohexen-1-one (Scheme 1). A subsequent route involved the use of the Wadsworth−Horner−Emmons reaction between the ylide of a *β*-ketophosphonate[11b−d] (**26** or **27**) and cyclohexanecarboxaldehyde **29** (Scheme 1). Both methods were quite flexible and allowed the introduction of a variety of lipophilic and polar side chains on the cyclohexane ring.

In the initial approach, the iodovinyl precursors **17** and **22** of the mixed homocuprates **18** and **23** were prepared as previously described from hexanoyl chloride[12a] and 5-phenylpentanoic acid,[12b] respectively. The mixed homocuprates **18** and **23** were obtained using the protected iodovinyl alcohols, **17** and **22** as transferable moieties.[13] This procedure involved formation of the cuprous acetylide from 3-methoxy-3-methyl-but-1-yne, halogen−metal exchange on the protected iodovinyl alcohols, and treatment of these organolithium reagents with the cuprous acetylide at low temperature. In situ addition of 2-cyclohexen-1-one on the thus obtained mixed homocuprates afforded the 3-substituted cyclohexanones **19** and **24 (**Scheme 1).

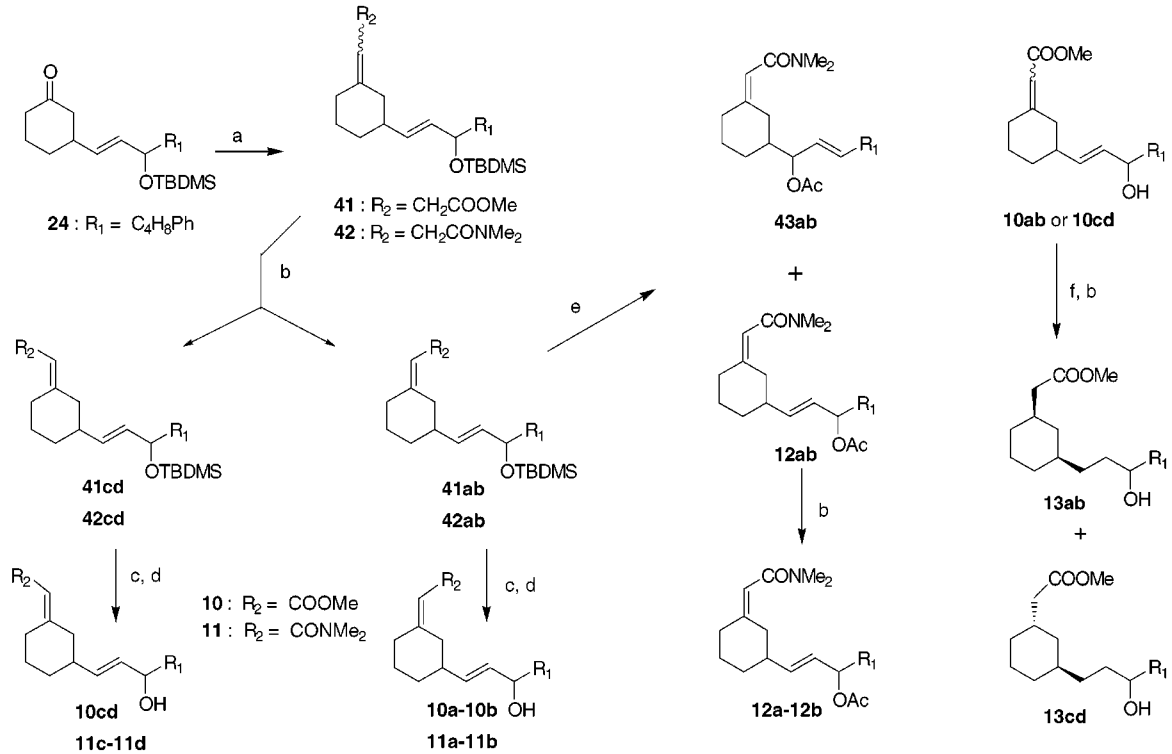
These two compounds were key intermediates in our synthetic strategy and have been used to introduce a variety of substituents, thus affording 1,3-disubstituted cyclohexanes with a number of different polar chains (Scheme 2). Condensation of the lithio derivative of 1-(3-bromopropyl)-4-methyl-(2,6,7)-trioxabicyclo[2.2.2]-octane[14] on the 3-substituted cyclohexanone **19**, followed by OBO ortho ester hydrolysis provided the hydroxy acid **20**, which was isolated as the corresponding lactone in 56% yield. A similar condensation of lithiated ethyl acetate on both **19** and **24** provided the hydroxy esters **21** and **25**, respectively, with a 92% yield in both cases. Each compound displayed three stereogenic centers and provided four racemic diastereoisomers (**a**, **b**, **c**, and **d**). The following general procedure was established as the most efficient for the purification of the four diastereoisomers: (i) Column chromatography or HPLC separation of the silylated ethers allowed the separation of a pair (**ab**) of trans isomers and a pair (**cd**) of cis isomers at the cyclohexyl ring (the trans isomers always being eluted first on silica gel). (ii) After deprotection of the alcohol by acidic hydrolysis, isolation of the four diastereoisomers (**a**, **b** trans and **c**, **d** cis by order of elution on normal phase) of compounds **1**−**3** could be achieved. (iii) Each hydroxy ester diastereoisomer was converted into its sodium salt by basic hydrolysis (NaOH/MeOH: H_2O) for further biological investigation. The two enantiomers **3bα** and **3b*β*** from the racemic mixture **3b** were also separated for evaluation, using a chiral HPLC column.

Scheme 2[a]



[a] Reagents: (a) **20**: $Br(CH_2)_3OBO$, *t*-BuLi, THF, −78 °C then 0.02N HCl, THF, 0 °C and LiOH, THF, rt, 56%; **21**, **25**, and **37**: CH_3CO_2Et, LDA, THF, −78 °C, 92, 92, and 87%, respectively; **38**: CH_3CONMe_2, LDA, THF, −78 °C, 86%; **39**: $CH_3CONMePh$, LDA, THF, −78 °C, 82%; **40**: $CH_3CON(n\text{-}Pr)_2$, LDA, THF, −78 °C, 87%. (b) Chromatoraphic separation. (c) 1 N HCl, THF, rt, 82−84%. (d) HPLC separation. (e) **8ab**: MnO_2/C, CH_2Cl_2, rt, 60%. (f) **9b**: H_2, 10% Pd/C, 1% $NaNO_2$, ethanol, rt, 87%. *Isolated as the lactone.

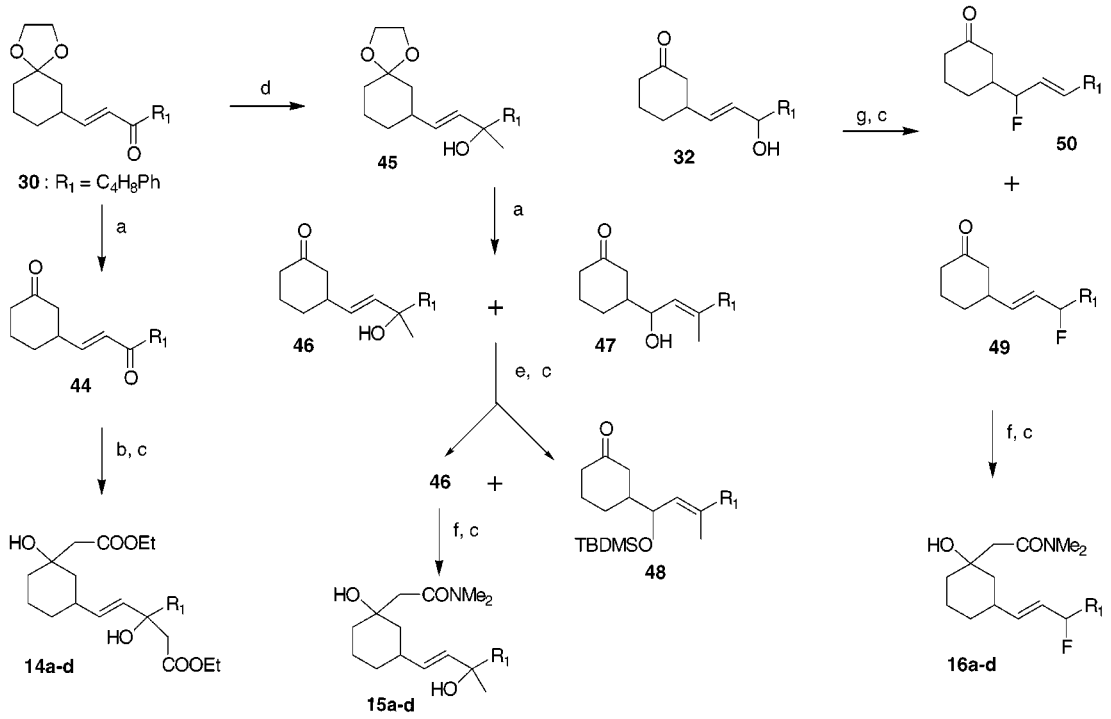
Scheme 3[a]



[a] Reagents: (a) **41**: methyl diethylphosphonoacetate, HNa, THF, rt, 96%; **42**: *N*,*N*-dimethylacetamide phosphonate, HNa, THF, rt, 91%. (b) HPLC separation, **41ab**−**41cd**: 32/68; **42ab**−**42cd**: 39/61. (c) 1N HCl, THF, rt, 92−96%. (d) HPLC separation (except for **10cd**). (e) $FeCl_3$−Ac_2O, **12ab**: 81%; **43ab**: 18%. (f) H_2, 10% Pd/C, 1% $NaNO_2$, ethanol, rt, 85%.

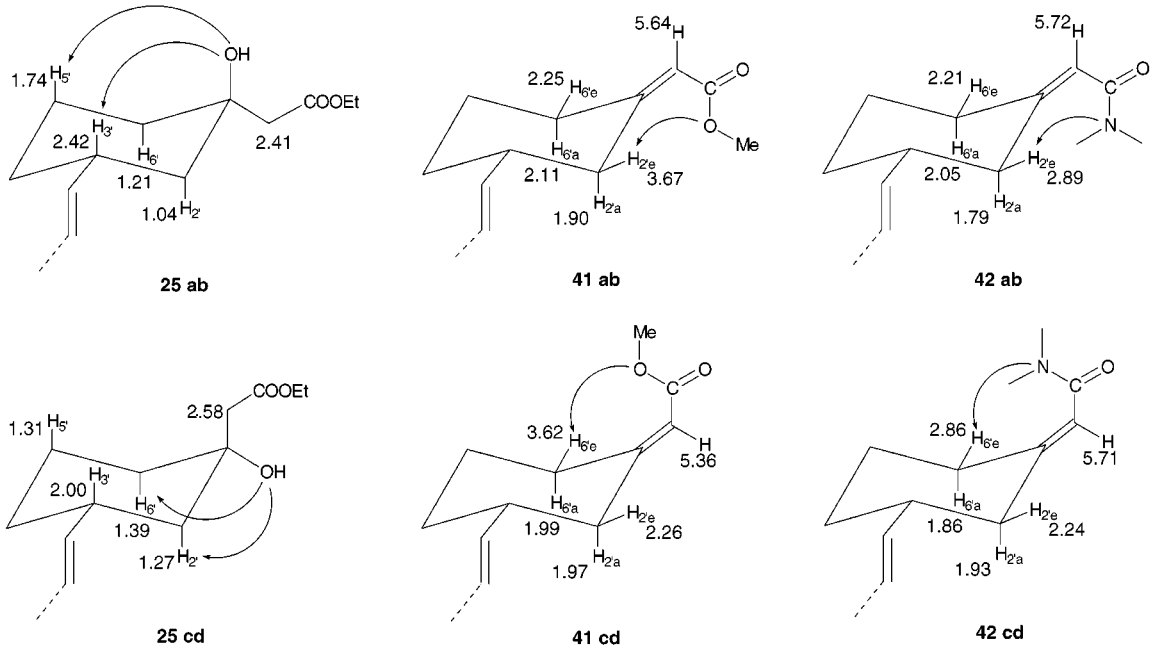
The relative configuration of trans and cis isomers at the 1,3-disubstituted cyclohexyl compounds was established by ^1H and two-dimensional NMR spectroscopy using the silylated ether intermediates (e.g., **25** in Chart 2). First the equatorial position of the bulky lipophilic chain was clearly established by the large coupling constants between $H_{3'}$ and both vicinal $H_{2'}$ and $H_{4'}$ (14.8 and 14.3 Hz, respectively), indicating an axial arrangement of all three protons. The respective trans and cis configurations could then be easily assigned, using the

Scheme 4[a]



[a] Reagents: (a) PPTS, acetone/H_2O, reflux, **44**: 96%; **46**: 58%; **47**: 14%. (b) CH_3COOEt, LDA, THF, −78 °C, 87%. (c) HPLC separation. (d) CH_3Li, diethyl ether, −35 °C to rt, 94%. (e) TBDMSCl, DBU, CH_2Cl_2, rt, **48**: 98%. (f) CH_3CONMe_2, LDA, THF, −78 °C, **15a**−**d**: 85%; **16a**−**d**: 84%. (g) MSTF, CH_2Cl_2, −50 °C, **49**: 56%; **50**: 26%.

Chart 2



influence of the axial or equatorial position of the quaternary hydroxyl substituent on the chemical shifts of the axial protons on the cyclohexyl ring. The axial protons $H_{3'}$ and $H_{5'}$ were more deshielded when the hydroxyl function was locked in an axial position, whereas $H_{2'}$ and $H_{6'}$ were more deshielded when the hydroxyl function was in an equatorial position.

The first synthetic route described above provided the target cyclohexanes **1**−**3** in reasonably good overall yields. However this methodology suffered from several drawbacks. First, it required the use of unstable intermediates such as halogeno vinyl ketones. Second, although the mixed homocuprate coupling was quite efficient on a small scale, it was more difficult to handle on the larger quantities required for SAR studies. This prompted us to explore another synthetic route to the key 3-substituted cyclohexanones **24** and **36**.

This alternate approach (Scheme 1) involved the Wadsworth−Horner−Emmons condensation[15] of the ylide of a β-ketophosphonate (**26** or **27**) on the carboxaldehyde **29**. These β-ketophosphonates were obtained, as previously[16] described, by condensation of 5-phenyl-

pentanoyl chloride (or nonanoyl chloride) on the organocopper derivative of diethyl methylphosphonate at low temperature. The required ketal ester **28** was prepared in three steps from methyl 3-hydroxybenzoate in 72% yield as described elsewhere.[17] Further reduction[15a] of the methyl ester using DIBAL-H in toluene at −78 °C afforded the protected 3-oxocyclohexane carboxyaldehyde **29**. This aldehyde could be isolated and characterized but not stored more than several hours.[11e] For this reason the reduction of the ester **28** had to be performed concomitantly to the formation of the ylide of the appropriate *β*-ketophosphonate (**26** or **27**) using sodium hydride in THF at −40 °C. The resulting crude aldehyde **29** was added on the appropriate ylide as soon as traces of alcohol were detected (after reduction of **29** for 30 min). According to this procedure, the corresponding α,*β*-unsaturated ketones **30** and **33** were prepared in 86% and 90% yield, respectively. As expected, the configuration of the double bond of these compounds, as established by ^{1}H NMR, proved to be *E* only (J_{trans} = 15.9 Hz), no trace of *Z* analogue being detected. The key intermediates **24** and **36** were then obtained in three steps from **30** and **33**, by 1,2-reduction of the α,*β*-unsaturated ketone using $NaBH_4$ in the presence of $CeCl_3$ which avoids parallel 1,4-reduction,[18] acidic deprotection of the carbonyl function using wet silica gel,[19] and protection of the allylic alcohol as a *tert*-butyldimethylsilyl ether.

This alternative route to intermediates **24** and **36** via *β*-ketophosphonates offered several advantages over the original approach using homocuprates. Primarily, the new route provided better overall yields (e.g., 45% for **24** from methyl 3-hydroxybenzoate[15b] instead of 14% from 5-phenylpentanoic acid[12b]). Moreover it involved stable intermediates that could be stored for a long time and reproducible reactions that could be scaled more easily. In addition, several of the intermediates generated in this procedure were used as starting materials in the preparation of other modified cyclohexanes required in our SAR study (cf. Schemes 3 and 4).

Condensation of the lithiated ethyl acetate on the carbonyl function of **36** led to the *β*-hydroxyester **37** from which were isolated four racemic diastereoisomers **4a**−**d** as previously described (Scheme 2). These isomers were converted to their sodium salts for biological evaluation. Similarly, a variety of lithiated acetamides were added to the 3-substituted cyclohexanone **24** and provided the *β*-hydroxyamides **38**−**40**. *N*,*N*-dimethylacetamides **5ab** and **5cd**, *N*-methyl-*N*-phenylacetamides **6ab** and **6cd**, and *N*,*N*-dipropylacetamide **7ab** were isolated by HPLC as mixtures of two racemic diastereoisomers each. Only the individual racemic diastereoisomers **5a** and **5b** in **5ab** were separated for further biological evaluation, as were the enantiomers **5bα** and **5b*β*** in **5b**.

Oxidation of the allylic alcohol of **3a** was achieved using manganese (IV) oxide on activated carbon and provided the α,*β*-unsaturated ketone **8ab** in 60% yield only, although no side product or starting material could be recovered (Scheme 2). This was probably due to partial substrate adsorption onto the carbon, but no yield enhancement was obtained by Soxhlet extraction. Palladium catalyzed hydrogenation of **3b** afforded the saturated derivative **9b** in 87% yield. A catalytic amount of sodium nitrite was found to be necessary in order to prevent the concomitant dehydroxylation of this compound.

Unsaturated analogues **10** and **11** of *β*-hydroxyester **3** and *β*-hydroxyamide **5** were synthesized in excellent yield by Wadsworth−Horner−Emmons condensation of the ylide of the appropriate phosphonates (methyl diethylphosphonoacetate[20] and *N*,*N*-dimethylamide derivative[21]) on the key 1,3-disubstituted cyclohexanone **24** (Scheme 3). HPLC separation of the silylated ethers **41** and **42** afforded, in each series, the *Z* (**41**−**42ab**) and *E* (**41**−**42cd**) isomers in a 32:68 and 39:61 ratio, respectively. The stereochemistry of these compounds was confirmed by NMR spectroscopy (Chart 2), the field effect of the ester oxygen or amide nitrogen selectively affecting the equatorial protons $H_{2'e}$ or $H_{6'e}$ in the *Z* or *E* configurations. After acidic hydroxyl deprotection, each racemic diastereoisomer could be isolated, except for the mixture **10cd** which could not be resolved. The enantiomers **10bα** and **10b*β*** in **10b** were further separated by chiral HPLC for subsequent bioassays.

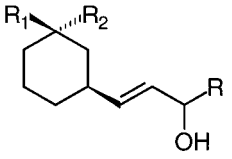
Acetylated derivatives **12a**,**b** of the ethylenic compounds **11a,b** were prepared by O-acylation of the silylated intermediate **42ab** using ferric chloride in acetic anhydride[22] (Scheme 3). Besides the expected acetylated compound **12ab** obtained in 81% yield, 18% of isomerized analogue **43ab** could be detected. The formation of the latter was explained by the generation of an allylic carbocation intermediate which allowed the migration of the double bond and attack of the acetate anion on the carbon α to the cyclohexyl ring. Separation of these two isomers and isolation of the two racemic diastereoisomers **43a** and **43b** was performed by preparative HPLC.

Fully saturated analogues of **10ab**−**10cd** were obtained by palladium catalyzed hydrogenation of **10cd** followed by HPLC separation of the cis and trans diastereoisomeric mixtures **13ab** and **13cd** formed in a 72/28 ratio. The relative cis configuration of the major isomer was established by NMR spectroscopy as previously described for the silylated *β*-hydroxyesters **1**−**3**, confirming that its formation was thermodynamically favored, due to the equatorial position of both its chains.

Scheme 4 outlines the preparation of the diester derivative **14** of *β*-hydroxyesters **3**, as well as the synthesis of methylated and dehydroxyfluorinated analogues **15** and **16** of the *β*-hydroxyamide **5**. Diester derivatives **14a**−**d** were obtained in two steps from the dioxolane intermediate **30** after deprotection of the cyclohexanone and condensation of the lithiated ethyl acetate on both carbonyl functions of **44**. The four racemic diastereoisomers of **14** were isolated by preparative HPLC, as described previously for **1**−**3**. The ratio of **14b** was surprisingly low compared to **14a**, **14c**, and **14d** (3% instead of 38%, 31%, and 28%, respectively), probably due to steric hindrance on one face of the α,*β*-unsaturated ketone when the short polar chain occupies the equatorial position.

Preparation of the methylated analogues **15** was achieved in a five-step procedure starting from dioxolane **30**. Introduction of the methyl substituent was performed in high yield by condensation of methyllithium on the α,*β*-unsaturated ketone of **30**. The only problematic step in this procedure was the acidic deprotection

Table 1. Effect of the Nature of the Polar Chain and Lipophilic Tail Lengths



Compd[a]	R	R_1	R_2	(IC_{50}, μM)[b,c]	pK_B (n)[d]
2a	C_5H_{11}	CH_2CO_2Na	OH	>10	
2b	C_5H_{11}	CH_2CO_2Na	OH	8 ± 0.7	5.10 (4)
2c	C_5H_{11}	OH	CH_2CO_2Na	>10	
2d	C_5H_{11}	OH	CH_2CO_2Na	10	5.25 (4)
3a	C_4H_8Ph	CH_2CO_2Na	OH	>10	
3b	C_4H_8Ph	CH_2CO_2Na	OH	0.8 ± 0.02	6.57 (7)
3bα	C_4H_8Ph	CH_2CO_2Na	OH	0.25 ± 0.06	6.19 (3)
3bβ	C_4H_8Ph	CH_2CO_2Na	OH	>10	
3c	C_4H_8Ph	OH	CH_2CO_2Na	>10	
3d	C_4H_8Ph	OH	CH_2CO_2Na	1.5	6.31 (7)
4a	C_8H_{17}	CH_2CO_2Na	OH	>10	
4b	C_8H_{17}	CH_2CO_2Na	OH	0.9	6.42 (5)
4c	C_8H_{17}	OH	CH_2CO_2Na	4	
4d	C_8H_{17}	OH	CH_2CO_2Na	2.5	
5a	C_4H_8Ph	$CH_2CO_2NMe_2$	OH	>10	
5b	C_4H_8Ph	$CH_2CO_2NMe_2$	OH	0.08 ± 0.03	6.91 (4)
5bα	C_4H_8Ph	$CH_2CO_2NMe_2$	OH	0.04 ± 0.01	7.50 (7)
5bβ	C_4H_8Ph	$CH_2CO_2NMe_2$	OH	>10	

[a] Carboxylic esters were tested into their sodium salts. [b] Inhibition of [^{3}H]LTB_4 (1nM) specific binding to human PMNs, assay performed as described in Experimental Section. [c] The IC_{50}'s for **2b**, **3b**, **3bα** **5b**, and **5bα** are the mean ± SEM of values obtained from at least distinct three assays. TheIC_{50}'s for **2d**, **3d**, **4b**, **4c**, and **4d** were obtained from two distinct dose-response curves with less than 15% variation. [d] Inhibition of LTB_4 induced chemotaxis of isolated human PMNs, assay performed as described in Experimental Section. pK_B were obtained from (n) various experiments.

of the carbonyl function of **45** which gave the expected tertiary alcohol **46** in only 56% yield along with the undesired isomerized compound **47** in 14% yield. Again, this was explained by the generation of a tertiary allylic carbocation after loss of H_2O in acidic medium. However, no attempt was made to optimize the reaction yield. The two isomers thus obtained could not be separated by HPLC due to similar polarities. Advantage was taken of their differences in reactivity toward a hydroxyl-protecting agent such as TBDMSCl to purify the mixture. Selective conversion of the secondary alcohol **47** to the silylated ether **48** gave the unreacted tertiary alcohol **46** in a straightforward manner. *β*-hydroxyamides **15a**−**d** were obtained by condensation of the lithiated *N*,*N*-dimethylacetamide on the carbonyl function of **46**, and subsequent HPLC purification as previously described for the isolation of the four *β*-hydroxyester diastereoisomers **3a**−**d**. In addition, chiral HPLC separation of both enantiomers **15bα** and **15bβ** of racemic compound **15b** was successfully achieved.

Dehydroxyfluorinated analogues **16a**−**d** were synthesized in two steps from the 3-substituted cyclohexanone **32**. Treatment of the allylic alcohol with morpholinosulfurtrifluoride[23] in dichloromethane at −50 °C provided the expected allylic fluoro derivative **49** along with its isomer **50** in an approximate 2:1 ratio. HPLC separation of these two constitutional isomers provided the required intermediate **49** which was converted, in 85% yield, to the *β*-hydroxyamides **16a**−**d**, following the procedure described for the preparation of **15a**−**d** from **46**.

Results and Discussion

The LTB_4 receptor affinities of the test compounds were determined by evaluating their ability to compete with the binding of [^{3}H]LTB_4 to receptors on intact human PMNs, the primary target inflammatory cells of interest. A few selected compounds were also tested for their ability to compete with the binding of [^{3}H]LTB_4 to receptors on guinea pig lung membranes. Most of the compounds were initially tested at 10 *μ*M versus 1 nM [^{3}H]LTB_4, and IC_{50} values were determined for the more potent compounds. The BLTR binding data obtained from these radioligand assays are summarized in Tables 1 and 2. Incubation of increasing concentrations of unlabeled LTB_4 resulted in a dose-dependent displacement of [^{3}H]LTB_4 from its specific binding sites with IC_{50} values of 8 nM and 2 nM, respectively, on human PMNs and guinea pig lung membranes. In addition, the LTB_4 antagonist activity of the most active compounds in the binding assays was established at the cellular level in two different functional assays. These compounds were evaluated for their ability to inhibit the LTB_4-induced chemotaxis of intact human PMNs in Boyden−Keller chambers and the LTB_4-induced guinea pig lung parenchymal strip contraction.

Our initial compound design utilized a structural template based upon one of the possible conformations[8] of LTB_4, its unstable triene unit being replaced by a cyclohexylene moiety that stabilizes the molecule and restricts its conformational freedom. This approach led to the synthesis of compound **1** (Scheme 2) possessing most of the other features of the native ligand: two hydroxyl groups in C_5 and C_{12} (LTB_4 numbering), a carboxylic acid function, and a lipophilic tail. Only the $C_{14}-C_{15}$ double bond of LTB_4 was not included, as it had previously been shown not to be critical for binding or functional activity.[24] As the initial compound **1b** only showed weak affinity for the LTB_4 receptor ($IC_{50} = 70$ μM), a SAR study was initiated in order to characterize the structural features that could enhance the binding to LTB_4 receptors. This study involved the length and chemical nature of the lipophilic tail and polar chains substituting the cyclohexane ring (Table 1) and an investigation of the relative importance on the binding affinity of the cyclohexylic (C_5) and allylic (C_{12}) hydroxyls (Table 2).

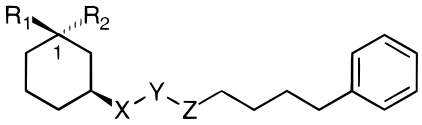
Very early in this study, it was discovered that within each series of dihydroxylated compounds **1**−**5**, the more polar trans diastereoisomers **b** were the most efficient at inhibiting the binding of [^{3}H]LTB_4 to receptors on human PMNs and guinea pig lung membranes. Interestingly, a similar result was obtained with unsaturated *Z* analogues **10b** and **11b**. This suggested that the relative configuration of the allylic hydroxyl on the lipophilic tail was a key feature for binding. This result correlated with an earlier study that had established that 12-epi-LTB_4 was 6 times less potent than LTB_4 in binding studies and 25 times less potent in functional assays.[25] Similarly, when mixtures of two racemic diastereoisomers were tested (**ab** or **cd**), the trans isomers (**ab**) were always more potent than the cis isomers (**cd**), indicating a receptor preference for the trans configuration. All together, these results establish the importance of the relative orientation of the allylic hydroxyl and the polar side chain for binding affinity, indicating that these two functions are strongly interacting with the receptor.

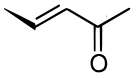
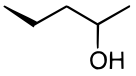
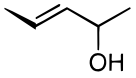
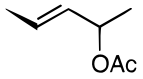
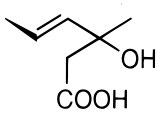
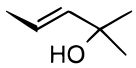
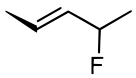
Initial modulation of **1** focused on optimizing the distance between the allylic hydroxyl and the carboxylic acid moiety, two structural elements required in the binding to the receptor. Shortening the polar chain of **1b** by two carbon units led to compound **2b** which displayed a higher affinity for the LTB_4 receptor ($IC_{50} = 8$ μM). On the basis of these results, the distance between the carboxylic acid and the allylic alcohol group of our disubstituted cyclohexanes was estimated to be an essential feature for receptor binding. For the first time (in this series), an antagonist functional activity was established at the cellular level on human PMNs with compound **2b** that blocks the LTB_4-induced chemotaxis with a pK_B value of 5.10. In vitro this compound also inhibited the LTB_4-induced contraction of guinea pig lung parenchymal strips with an IC_{50} value of 0.3 μM.

Previous work had demonstrated that any modification in the length of the lipophilic tail of the native LTB_4 ligand correlated with a dramatic loss in binding affinity.[26] For this reason we thought it would be of interest to elongate by four carbon units the lipidic tail of compound **2b** in order to obtain a compound with a lipophilicity similar to that of LTB_4. This simple homologation provided compound **4b** which, not surprisingly, showed a 10-fold increase of the binding affinity ($IC_{50} = 0.9$ μM).

Several studies have described ω-oxidation as being one of the major metabolic pathways of LTB_4 leading to loss of biological activity.[27] It was anticipated that the introduction of an aromatic ring at the end of the lipidic tail of our compounds would thus enhance their metabolic resistance by preventing ω-oxidation. The effective in vivo activity would therefore be increased. A similar aryl group substitution performed on prostaglandin analogues precluded metabolism and led to derivatives with higher activity and selectivity.[28] This modification was achieved on compound **2** in order to obtain an analogue of similar lipophilicity to compound **4**. With IC_{50} values of 0.8 μM on human PMNs, the

Table 2. Analogues with Variation at Allylic Hydroxyl (X−Y−Z) and C_1 Hydroxyl Group Domains



Compd[a]	X−Y−Z	R_1, R_2	LTB_4 receptor binding[b] (IC_{50}, μM)
8ab		CH_2CO_2Na, OH	> 10
9b		CH_2CO_2Na, OH	5.3[c]
13ab		CH_2CO_2Na, H	2.6
10a		= $CHCO_2Na$	>10
10b		= $CHCO_2Na$	1.3
10bα		= $CHCO_2Na$	0.5
10bβ		= $CHCO_2Na$	>10
11a		= $CHCO_2NMe_2$	7
11b		= $CHCO_2NMe_2$	1
12b		= $CHCONMe_2$	>10
14b		CH_2CO_2Na, OH	> 10
15b		CH_2CONMe_2, OH	7
15bα		CH_2CONMe_2, OH	>10
15bβ		CH_2CONMe_2, OH	4.5
16a		CH_2CONMe_2, OH	2
16b		CH_2CONMe_2, OH	6.5

[a,b] See Table 1. [c] The IC_{50}'s were obtained from two distinct dose−response curves with less than 15% variation.

phenyl-substituted compound **3b** was equipotent in comparison to its linear analogue **4b**, indicating that addition of an aromatic ring did not introduce any negative interaction within the receptor. However, due to its expected superior ability to resist metabolic degradation in vivo, compound **3b** was preferred to **4b** for further structural modifications.

One of the isolated enantiomers **3bα** displayed higher receptor affinity than the previously tested racemic compounds (IC_{50} = 250 nM), whereas the other enantiomer (**3bβ**) was not recognized by the LTB_4 receptor. This result clearly indicates the high stereospecificity of our disubstituted cyclohexanes for the LTB_4 receptor. It is possible that the active enantiomer **3bα** has the same *R* configuration at C_{12} as the native ligand, but this needs to be determined.

The antagonist activity of compound **3b** was demonstrated at the cellular level on human PMNs in a LTB_4-induced chemotaxis assay. As expected, the gain in affinity of **3b** over **2b** was accompanied by an enhancement of antagonist activity (pK_B = 6.57). This compound also inhibited the contractile effect of LTB_4 on guinea pig lung parenchymal strips (IC_{50} = 40 nM). In a phorbol-12-myristate-13-acetate (PMA)-induced ear oedema test, **3b** exhibited potent antiinflammatory activity (56% of inhibition at 60 μg/ear vs 50% of inhibition at 10 μg/ear for dexamethasone) when applied topically 30 min prior to the application of PMA. This effect is probably related to LTB_4 antagonism, since **3b** did not show any ability to inhibit either the 5-lipoxygenase or cyclooxygenase (COX1 and COX2) activities at concentrations up to 10 μM. Similarly **3b** was inactive against LTD_4-induced guinea pig ileum contraction at up to 10 μM. Therefore compound **3b** is characterized by a specific LTB_4 antagonist activity.

Subsequent efforts were directed toward examining the effect on the binding affinity of modifying the carboxylic acid moiety of our analogues with various acetamide functions (Table 1). A previous study indicated that such a replacement could be beneficial for receptor binding, since the *N*-methyl-*N*-phenethylacetamide, moiety of the LTB_4 antagonist RG14893 appeared as a key feature for its high binding affinity.[29] This observation prompted us to prepare the *N*,*N*-dimethylacetamide, *N*-methyl-*N*-phenylacetamide and *N*,*N*-dipropylacetamide derivatives of compound **3** (respectively **5**, **6**, and **7**).

Replacement of the carboxylic acid moiety for an *N*,*N*-dimethylacetamide function proved to be beneficial for the binding affinity. With an IC_{50} value of 80 nM, the isolated racemic diastereoisomer **5b** displayed a 10-fold enhancement of its affinity compared to that of the **3b** analogue. This increase in affinity was unexpected as a similar modification of the native ligand provided the *N*,*N*-dimethylamide-LTB_4 which only competed for the low affinity binding sites of LTB_4.[24b]

Evaluation of both enantiomers of **5b** provided one high affinity compound **5bα** (IC_{50} = 40 nM) while **5bβ** did not show any affinity for the LTB_4 receptor. This result correlated well with the one previously obtained with the β-hydroxyester **3bα**, confirming the high stereospecificity of these cyclohexane derivatives for the LTB_4 receptor. The antagonist activity of **5bα** was further established in a LTB_4-induced human PMN chemotaxis assay where it displayed a pK_B value of 7.50. This clearly confirmed that our *N*,*N*-dimethylacetamide derivatives could compete with the high affinity LTB_4 binding sites in the receptor that are responsible for the chemotactic response. In contrast, *N*,*N*-dimethylamide-LTB_4 was only shown to be a moderate antagonist of the LTB_4-induced degranulation of rabbit or rat PMNs, displaying partial agonist activity at higher concentrations and therefore possibly acting by a desensitization mechanism.[30,24a] The other acetamide moieties investigated here did not provide the same magnitude of affinity increase over the carboxylic acid function.

Additional studies focused on determining the role of the C_1 hydroxyl element on receptor binding. It was established in a previous study that the C_5 hydroxyl group of LTB_4 was not a requirement for receptor binding, since the 5-deoxy-LTB_4 retains the high affinity binding of the native ligand.[25] Moreover, the 60 times weaker binding affinity of 5-epi-LTB_4 supported the hypothesis that inversion of configuration at C_5 could introduce an unfavorable interaction with the receptor. It was thus anticipated that a similar negative interaction could be responsible for a loss in the affinity of our dihydroxylated compounds. This led us to remove the C_1 hydroxyl from compounds **3** and **5** and synthesize the unsaturated derivatives **10** and **11**. Compound **10b** (Table 2) displayed a similar potency as its β-hydroxy-acid analogue **3b**, indicating that the C_1 hydroxyl is not required for binding to the receptor. This was confirmed by the similar potency of the fully saturated derivative tested as a mixture of two diastereoisomers **13ab**, which displayed higher binding affinity than the isolated hydroxylated analogue isomer **9b**. Again one of the isolated enantiomers of **10b** displayed higher receptor affinity than the racemic, while the other one, **10bβ**, was not recognized by the receptor. However, in the *N*,*N*-dimethylacetamide series, compound **11b** did not retain the high affinity of its dihydroxylated analogue **5b**, possibly because of the restricted orientation of the amide function due to the presence of the exocyclic double bond. Altogether, these results concerning compounds **10** and **11** led to the conclusion that no negative interaction was introduced by the presence of the C_1 hydroxyl in our initial design (unless the observed inferior binding affinity of cis diastereoisomers compared to trans diastereoisomers was actually a reflection of this negative interaction).

Further efforts were aimed at confirming the key role of the allylic hydroxyl moiety on receptor binding. To this end several structural modifications of and around this function were investigated (Table 2). Oxidation of the alcohol in **3b** provided the α,β-unsaturated ketone **8ab** which did not retain any of the binding affinity of its hydroxylated precursor. Similarly, saturation of the double bond provided the derivative **9b** which displayed only one-fifth of the affinity observed with its unsaturated analogue **3b**, suggesting that an adjacent planar structure is required for correct orientation of the hydroxyl group. Taken together these results clearly identified the allylic alcohol pharmacophore of our initial design as an essential structural element. These results were in agreement with earlier studies establishing the presence of the C_{12} hydroxyl as a key feature for binding to the receptor, due to the fact that 12-deoxy-LTB_4 is

more than 2 orders of magnitude less efficient in the binding and chemotaxis assays.[25] In addition, 10,11-dehydro-LTB_4 and 10,11-dehydro-12-oxo-LTB_4 have been identified in earlier studies as metabolites of LTB_4 from the reductase-dehydrogenase pathway with reduced or no activity.[31]

O-Acylation of the allylic hydroxyl of the unsaturated compound **11b** led to derivative **12b** with no affinity for the LTB_4 receptor, again indicating the necessity for a hydrogen bond donor substituent or tight steric requirements of the binding site. However this result was somewhat unexpected as the diacetyl-LTB_4 had previously been described as a competitive inhibitor of LTB_4-induced chemotaxis of human PMNs at equimolar concentrations with LTB_4.[32]

Introduction of a second carboxylic acid function in LTB_4 antagonists has recently been the focus of several studies.[31d] This structural modification provided analogues with enhanced binding affinity, suggesting the existence of two acid sites within the receptor protein. With this in mind, we introduced a second carboxylic acid group on C_{12} of compound **3**, postulating that this function would interact with the binding site usually occupied by the allylic hydroxyl. The resulting derivative **14** did not show any affinity for the BLTR, clearly indicating that the allylic hydroxyl could not be replaced with a carboxylic function in this series.

Given the key role of the allylic hydroxyl in this series of 1,3-disubstituted cyclohexanes, the last structural modifications were aimed at enhancing their metabolic stability toward the reductase-dehydrogenase pathway. To this end, it was postulated that introduction of a methyl group at C_{12} would prevent the oxidation of the allylic hydroxyl, thus providing a metabolically stable analogue of **5**. Such a modification has previously been used to provide 12(*R*)-methyl-LTB_3 as a potent agonist of LTB_4 with a binding affinity similar to that of LTB_3.[33] Surprisingly, the methylated derivative **15b** did not retain the high affinity of its precursor **5b**. Further isolation of the enantiomer **15b*β*** did not provide any affinity enhancement. This result suggested that the newly introduced methyl substituent prevented the key interaction of the allylic hydroxyl group with the receptor protein.

In a further attempt to obtain an analogue with increased metabolic stability toward the reductase-dehydrogenases, the allylic hydroxyl was replaced with a fluoro group in **16**. Fluorinated derivatives are often used to reduce the metabolism of hydroxylated compounds as they are not subjected to oxidation.[34] The fluoro group is usually an excellent bioisostere for hydroxyl functions as most of the physicochemical parameters of oxygen and fluoro atoms are similar (bond length, electronegativity). In addition, if steric effects were here partly responsible for the reduced affinity of **12**, **14**, and **15**, the smaller fluoro group may be advantageous. When evaluated in receptor binding assays, the fluoro analogues did exhibit some affinity for the LTB_4 receptor ($IC_{50} = 2\ \mu M$ for **16a**), but did not fully retain the potency of their hydroxylated analogues **5**. Again, one possible explanation for this partial loss of affinity could be the requirement for a hydrogen bond donor substituent, in contrast to the fluoro group.

Conclusion

We have developed novel LTB_4 receptor ligands based on the introduction of a central cyclohexylene system as a stable substitute for the triene unit of LTB_4. To our knowledge, this is the first time that high affinity LTB_4 antagonists have been developed upon introduction of a 1,3-disubstituted cyclohexane and not an aromatic/heteroaromatic ring in place of the triene moiety. Our SAR studies, based on in vitro receptor binding assays, have established that the spatial relationship between the carboxylic acid and the allylic hydroxyl functions is crucial for receptor binding. Compounds **3bα** and **5bα** are stable analogues that display high affinities for LTB_4 receptors on human PMNs and antagonist profiles with no detectable agonist activity. They have been selected for further evaluation. This series of 1,3-disubstituted cyclohexanes provides rigid mimics of the natural ligand which should prove useful as biological tools and may lead to significant advances in our knowledge of the structural organization of the receptor protein. The LTB_4 receptor with the amino acid sequence reported by Yokomino et al.[6a] has been expansed in *Escherichia coli*, and its interaction with the antagonist **5bα** is being characterized at the structural level.[6b] In addition it provides a framework for designing novel leukotriene antagonists which may be useful for a variety of inflammatory diseases.

Experimental Section

Chemical Methods. Melting points (uncorrected) were measured in open capillary tubes on a Büchi Tottoli melting point apparatus. Mass spectra (MS) were recorded on a JEOL DX-300 mass spectrometer or on a JEOL SX-102 mass spectrometer at Laboratoire de Mesures Physiques de l'Université Montpellier II. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained at room temperature on a Bruker AMX-360 or AC-100 instrument with the solvents indicated. All ^{1}H NMR chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS, δ 0.00) as the internal standard. Assignments were made using ^{13}C, homonuclear, and heteronuclear bidimensional NMR. ^{31}P NMR spectra were recorded on a Bruker WP-200SY instrument using phosphoric acid as internal standard. ^{19}F NMR spectra were obtained on a Bruker AC-250 instrument. Infrared (IR) spectra were recorded on a Beckmann Acculab-2 spectrophotometer using samples as liquid films on sodium chloride cells. Maximum absorption frequencies are reported in cm^{-1}. UV spectra were obtained on a Varian Super Scan 2 spectrophotometer. Specific rotation values were determined on a Perkin-Elmer 247 polarimeter at 589 nm. Elemental analyses were performed by Service Central d'Analyses du CNRS (Vernaison, France) and were within $\pm$0.40% of the calculated values. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel $60F_{254}$ aluminum-backed plates. HPLC purifications were performed on Waters HPLC equipment (Model 590 pump, Model 481 LC spectrophotometer) at room temperature using Rsil (10 μm, 22 $\times$ 250 mm), Inertsil (5 μm, 20 $\times$ 250 mm), Nucleosil (10 μm, 10 $\times$ 250 mm) or Chiralcel-OD (5 μm, 10 $\times$ 250 mm) columns with the solvents described. UV detection was made at 260 nm. Chemicals used in this study were obtained from Aldrich and solvents from SDS. Tetrahydrofuran (THF) was fresly distilled from sodium-benzophenone, methanol from sodium, cyclohexane from KOH, dichloromethane from $CaCl_2$ and then from CaH_2, and ethyl acetate from CaH_2. All reactions were carried out under nitrogen, and crude products were purified by chromatography using Gerudan SI 60 neutral silica gel (70−230 mesh) with the solvents described. Nomenclature for the prepared compounds is given following the IUPAC rules for the nomenclature of organic

compounds. All tested compounds bearing an ester function were tested as sodium salts after saponification.

3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-oct-1-en-1-yl]cyclohexanone (19). A solution of compound **17**[12a] (2.21 g, 6 mmol) in dry diethyl ether (50 mL) was cooled to −78 °C and treated with a 1.54 M solution of *n*-butyllithium in hexane (3.9 mL, 6 mmol). The mixture was stirred for 2 h at −78 °C. In parallel, the cuprous acetylide was prepared[10,13] from a stirred and cooled to −50 °C solution of 3-methoxy-3-methyl-but-1-yne (0.588 g, 6 mmol) in dry diethyl ether (25 mL), to which was added dropwise *n*-butyllithium 1.54 M in hexane (3.9 mL, 6 mmol). At the end of the addition, the mixture was brought back to −10 °C in 15 min and kept at this temperature for 15 min. Dry copper bromide−methyl sulfide complex (1.235 g, 6 mmol) was then added at −20 °C. A yellow coloration was immediately observed, which rapidly turned to orange. After 30 min of stirring between −20 °C and −15 °C, the suspension of copper salt had disappeared. The cuprous acetylide was progressively added under nitrogen via a transfer needle to a −78 °C solution of the silylated organolithium derivative. The pale orange medium was brought back to −45 °C in 30 min and kept at this temperature during 45 min to become pale yellow. A solution of 2-cyclohexen-1-one (0.377 g, 3.3 mmol) in dry THF (2 mL) was added dropwise to the −78 °C resulting solution of the mixed cuprate **18**. The golden yellowish medium was brought back to −60 °C and became red-orange after 2 h at this temperature. After a cold hydrolysis with saturated NH_4Cl, diethyl ether (50 mL) was added and the reaction mixture was filtered through Celite. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with distilled water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with cyclohexane/diethyl ether (90/10) afforded the title compound **19** (0.985 g, 2.90 mmol) in 88% yield: ^{1}H NMR (60 MHz, CCl_4) δ 5.40 (m, 2H, $H_{1''}$ and $H_{2''}$), 4.05 (m, 1H, $H_{3''}$), 2.23−1.83 (m, 9H, $H_{2'}$-$H_{6'}$), 1.3 (m, 8H, $H_{4''}$-$H_{7''}$), 0.91 (m, 12H, Si-*t*-Bu and $H_{8''}$), 0.0 (m, 6H, Si-CH_3); IR (film) 1705; MS (IE, 20 eV) *m*/*z* 281 (M − *t*-Bu). Anal. ($C_{20}H_{38}O_2Si$) C, H, O.

3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane-6-spiro-*δ*-valerolactone (20). To a stirred solution of (3-bromopropyl)-4-methyl(2,6,7)-trioxabicyclo[2.2.2]-octane[14] (2.1 g, 8.366 mmol) in dry THF (30 mL) under nitrogen at −78 °C was added dropwise over 20 min a 1.8 M solution of *tert*-butyllithium in pentane (9.3 mL, 16.7 mmol). The reaction mixture was stirred for 30 min at −60 °C and then cooled to −78 °C. A solution of **19** (2.38 g, 8.366 mmol) in dry THF (10 mL) was added dropwise over 10 min, and the temperature was slowly allowed to rise to room temperature during the 4 h of stirring. The medium was hydrolyzed with ice-cold water (10 mL), the aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with distilled water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oily residue (4.5 g) which was chromatographed on silica gel pretreated with 10% triethylamine in cyclohexane. Elution of diethyl ether containing 1% triethylamine afforded 2.810 g of the expected OBO ortho ester which was dissolved in THF (50 mL). A 0.02 N solution of HCl (12 mL, 0.24 mmol) was added dropwise at 0 °C for selective deprotection. After 40 min of stirring at room temperature, the reaction was quenched with saturated Na_2CO_3. The reaction mixture was extracted with diethyl ether, and the combined organic layers were dried over anhydrous sodium sulfate. After evaporation of the solvent, the intermediate ester was dissolved in THF (100 mL) and a 0.1 N solution of LiOH (60 mL) was added. Stirring was continued for 2 h, and the medium was acidified with a 0.1 N solution of HCl. After diethyl ether extraction, the combined organic layers were washed with distilled water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded a residue which was chromatographed on silica gel. Elution of cyclohexane/diethyl ether (70/30) afforded the title compound **20** (1.911 g, 4.685 mmol) in 56% yield. Further preparative HPLC chromatography (10 μm Rsil, 22 × 250 mm, cyclohexane/diethyl ether: 65/35, 10 mL/min; **20ab**: 26 min; and **20cd**: 36 min) provided compounds **20ab** (0.730 g, 1.789 mmol) and **20cd** (0.890 g, 2.181 mmol).

(1*S,3*S**)-3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane-6-spiro-*δ*-valerolactone (20ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.37 (m, 2H, $H_{1''}$ and $H_{2''}$), 3.96 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.52 (m, 1H, $H_{3'}$), 2.45 (t, 2H, J = 6.4 Hz, H_3), 1.95−0.90 (m, 20H, H_4−H_5, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.84 (m, 12H, Si-*t*-Bu and $H_{8''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 1730. Anal. ($C_{24}H_{44}O_3Si$) C, H, O.

(1*R,3*S**)-3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane-6-spiro-*δ*-valerolactone (20cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.36 (m, 2H, $H_{1''}$ and $H_{2''}$), 3.95 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.46 (m, 2H, H_3), 2.02 (m, 1H, $H_{3'}$), 1.90−0.95 (m, 20H, H_4-H_5, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.85 (m, 12H, Si-*t*-Bu and $H_{8''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 1730. Anal. ($C_{24}H_{44}O_3Si$) C, H, O.

Ethyl 1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane Acetate (21). To a 1.59 M solution of *n*-butyllithium in hexane (6.8 mL, 10 mmol) at −80 °C under nitrogen in a 1-L three-necked flask was added dropwise in 30 min a solution of freshly distilled diisopropylamine (1.165 g, 11.52 mmol) in dry THF (40 mL). The medium was stirred for 40 min at −78 °C, and freshly distilled ethyl acetate (0.996 g, 11.268 mmol) in dry THF (7 mL) was added dropwise in 30 min. After 30 min of stirring at −78 °C, compound **19** (2.106 g, 6.23 mmol) in dry THF (15 mL) was added dropwise. The temperature was slowly allowed to rise to room temperature during the 16 h of stirring after which the mixture was hydrolyzed with ice-cold water (10 mL). The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with distilled water (2 × 50 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oily residue (2.7 g) which was chromatographed on silica gel. Elution of cyclohexane/diethyl ether (92/8) afforded separation of the two isomers **21ab** (1.194 g, 2.80 mmol) and **21cd** (1.220 g, 2.86 mmol) in 45% and 46% yield, respectively.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane Acetate (21ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.41 (ABXY, 1H, J = 15.9 Hz and J = 5.8 Hz, $H_{1''}$), 5.33 (ABXY, 1H, J = 15.9 Hz and J = 5.8 Hz, $H_{2''}$), 4.16 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 3.97 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.32 (m, 1H, OH), 2.40 (s, 2H, H_2), 2.38 (m, 1H, $H_{3'}$), 1.80−0.90 (m, 16H, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 1.26 (t, 3H, J = 7.2 Hz, CH_3), 0.86 (m, 12H, Si-*t*-Bu and $H_{8''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 3500, 1720. Anal. ($C_{24}H_{46}O_4Si$) C, H, O.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-oct-1-en-1-yl]-1-cyclohexane Acetate (21cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.41 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.33 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.22−4.12 (m, 2H, CH_2CH$_3$), 3.98 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.79 (s, 1H, OH), 2.58 (d, J = 15.0 Hz, 2H, H_2), 2.02 (m, 1H, $H_{3'}$), 1.80−0.95 (m, 16H, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 1.26 (t, 3H, J = 7.2 Hz, CH_3), 0.85 (m, 12H, Si-*t*-Bu and $H_{8''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 3500, 1720. Anal. ($C_{24}H_{46}O_4Si$) C, H, O.

3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexanone (24). Procedure from **22** via the mixed cuprate **23**: Compound **24** was prepared from **22**[12b] according to the procedure described for **19**. Purification by column chromatography (eluent: cyclohexane/diethyl ether (96/4)) afforded the title compound **24** in 75% yield.

Procedure from **32**: A stirred solution of *tert*-butyldimethylsilyl chloride (19.3 g, 128 mmol) and DBU (23.37 g, 153.5 mmol) in dry dichloromethane (160 mL) was cooled to 0 °C under nitrogen. A solution of the compound **32** (30.5 g, 106.64 mmol) in dry dichloromethane (100 mL) was added dropwise, and the mixture was stirred for 48 h at room temperature. The reaction was hydrolyzed with distilled water and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with 0.1 N HCl, saturated $NaHCO_3$, and distilled water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was

purified by column chromatography (eluent: cyclohexane/diethyl ether, 97/3) to afford the title compound **24** (40.1 g, 100.2 mmol) in 94% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.47 and 5.46 (ABXY, J = 15.5 Hz and J = 6.0 Hz, 1H, $H_{1''}$), 5.38 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 3.99 (t, J = 6.0 Hz, 1H, $H_{3''}$), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.45 (m, 1H, $H_{3'}$), 2.40 (d, J = 13.6 Hz, 1H, $H_{2'e}$), 2.35 (d, J = 12.6 Hz, 1H, $H_{6'e}$), 2.25 (td, J = 11.8 Hz and J = 5.8 Hz, 1H, $H_{6'a}$), 2.15 (t, J = 12.7 Hz, 1H, $H_{2'a}$), 2.03 (d, J = 13.6 Hz, 1H, $H_{5'e}$), 1.88 (d, J = 13.6 Hz, 1H, $H_{4'e}$), 1.67 (q, J = 14.6 Hz, 1H, $H_{5'a}$), 1.59 (quint, J = 7.7 Hz, 2H, $H_{6''}$), 1.46 (qd, J = 13.1 Hz and J = 4.0 Hz, 1H, $H_{4'a}$), 1.44 (m, 2H, $H_{4''}$), 1.31 (m, 2H, $H_{5''}$), 0.86 (s, 9H, Si-*t*-Bu), −0.01 and 0.00 (s, 6H, Si-CH_3); IR (film) 1710; MS (FAB$^+$): *m*/*z* 343 (M^+ − *t*-Bu, 62). Anal. ($C_{25}H_{40}O_2Si$) C, H.

Ethyl 1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (25). Compound **25** was prepared from **24** according to the procedure described for **21**. Elution on silica gel (cyclohexane/diethyl ether: 92/8) afforded a first separation of the two isomers **25ab** and **25cd** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/diethyl ether: 92/8, 12 mL/min; **25ab**: 26 min; and **25cd**: 36 min). After HPLC chromatography, compounds **25ab** (12.9 g, 26.39 mmol) and **25cd** (15.0 g, 30.69 mmol) were isolated in, respectively, 42.5% and 49.5% yield.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (25ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.41 and 5.42 (ABXY, 1H, J = 15.9 Hz and J = 5.8 Hz, $H_{1''}$), 5.34 (ABXY, 1H, J = 15.9 Hz and J = 5.8 Hz, $H_{2''}$), 4.17 (q, 2H, J = 7.1 Hz, CH_2CH_3), 3.99 (q, 1H, J = 6.2 Hz, $H_{3''}$), 3.20 (s, 1H, OH), 2.58 (t, 2H, J = 7.7 Hz, $H_{7''}$), 2.42 (m, 1H, $H_{3'}$), 2.41 (s, 2H, H_2), 1.76 (d, 1H, J = 13.4 Hz, $H_{2'e}$), 1.74 (m, 1H, $H_{5'a}$), 1.73 (d, 1H, J = 13.4 Hz, $H_{6'e}$), 1.73 (m, 1H, $H_{4'e}$), 1.60 (m, 2H, $H_{6''}$), 1.56 (m, 1H, $H_{5'e}$), 1.46 (m, 2H, $H_{4''}$), 1.33 (m, 2H, $H_{5''}$), 1.26 (t, 3H, J = 7.1 Hz, CH_3), 1.21 (td, 1H, J = 14.4 Hz and J = 4.3 Hz, $H_{6'a}$), 1.04 (t, 1H, J = 14.8 Hz, $H_{2'a}$), 0.94 (qd, 1H, J = 14.3 Hz and J = 3.7 Hz, $H_{4'a}$), 0.87 (s, 9H, Si-*t*-Bu), 0.01 and −0.01 (s, 6H, Si-CH_3); IR (film) 3500, 1710; MS (FAB$^+$) *m*/*z* 339 (M − H_2O − OTBDMS). Anal. ($C_{29}H_{48}O_4Si$) C, H.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (25cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.40 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.32 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.17 (q, J = 7.3 Hz, 2H, CH_2CH_3), 3.98 (q, J = 5.6 Hz, 1H, $H_{3''}$), 3.79 (s, 1H, OH), 2.58 (t, J = 7.2 Hz, 2H, $H_{7''}$), 2.58 (s, 2H, H_2), 2.00 (m, 1H, $H_{3'}$), 1.76 (d, J = 13.7 Hz, 1H, $H_{2'e}$), 1.76 (d, J = 13.7 Hz, 1H, $H_{6'e}$), 1.72 (m, 1H, $H_{5'e}$), 1.65 (m, 1H, $H_{4'e}$), 1.60 (m, 2H, $H_{6''}$), 1.45 (m, 2H, $H_{4''}$), 1.39 (t, J = 13.1 Hz, 1H, $H_{6'a}$), 1.32 (m, 2H, $H_{5''}$), 1.31 (m, 1H, $H_{5'a}$), 1.27 (t, J = 14.8 Hz, 1H, $H_{2'a}$), 1.26 (t, J = 7.3 Hz, 3H, CH_3), 1.00 (qd, J = 14.3 Hz and J = 3.7 Hz, 1H, $H_{4'a}$), 0.85 (s, 9H, Si-*t*-Bu), 0.00 and −0.02 (s, 6H, Si-CH_3); IR (film) 3500, 1710; MS (FAB$^+$) *m*/*z* 339 (M − H_2O − OTBDMS). Anal. ($C_{29}H_{48}O_4Si$) C, H, O.

1,1-Ethylenedioxy-3-[(*E*)-3-oxo-7-phenyl-1-hepten-1-yl]-cyclohexane (30). A stirred solution of diethyl-2-oxo-6-phenylhexylphosphonate **26** (36.4 g, 116.7 mmol) in dry THF (420 mL) under nitrogen in a 2 L three-neck round-bottom flask was treated portionwise with sodium hydride 50% suspension in mineral oil (5.6 g, 116.7 mmol). Formation of the ylide of the β-ketophosphonate was immediate as a yellow coloration could be observed. In parallel, to a stirred solution of ester **28** (21 g, 105 mmol) in dry toluene (420 mL) under nitrogen at −80 °C in a 1 L three-neck round-bottom flask was added dropwise in 1 h a 1 M solution DIBAL-H (105 mL, 105 mmol) in toluene. The formation of the aldehyde **29** was followed by GC, and traces of overreduction could be detected after 30 min. This solution of aldehyde at −78 °C was added dropwise in 20 min via a transfer needle to the solution of ylide cooled to −35 °C. The cooling bath was removed and the reaction mixture allowed to warm to room temperature in 40 min and stirred for 16 h. The medium was hydrolyzed with brine and stirred for 1 h 30. The reaction mixture was filtrated over Celite and the cake washed with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, a yellow oil (36.2 g) was obtained containing the title compound **30** and a small amount of unreacted ester **28** (4%) and unreacted β-ketophosphonate **26** (11.5%). The ester was distilled off under reduced pressure ($bp_{0.01}$ = 60−70 °C). The residue was then chromatographed on silica gel. Elution of cyclohexane/diethyl ether (80/20) afforded the title compound **30** (29.5 g, 90 mmol) in 86% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 6.71 (ABX, 1H, J = 16.0 Hz and J = 6.8 Hz, $H_{1''}$), 6.02 (ABX, J = 16.0 Hz and J = 1.2 Hz, 1H, $H_{2''}$), 3.91 and 3.92 (s, 4H, H_1 and H_2), 2.60 (t, J = 7 Hz, 2H, $H_{7''}$), 2.52 (t, J = 3.5 Hz, 2H, $H_{4''}$), 2.44 (m, 1H, $H_{3'}$), 1.79 (m, 1H, $H_{2'e}$), 1.77 (m, 1H, $H_{5'e}$), 1.74 (m, 1H, $H_{4'e}$), 1.73 (m, 1H, $H_{6'e}$), 1.63 (m, 2H, $H_{5''}$), 1.63 (m, 2H, $H_{6''}$), 1.49 (q, J = 14.4 Hz, 1H, $H_{5'a}$), 1.44 (td, J = 13.2 Hz and J = 4.0 Hz, 1H, $H_{6'a}$), 1.36 (t, J = 12.6 Hz, 1H, $H_{2'a}$), 1.08 (qd, J = 12.8 Hz and J = 4.0 Hz, 1H, $H_{4'a}$); IR (film) 1690, 1630, 970; MS (FAB$^+$) *m*/*z* 329 (M + H^+). Anal. ($C_{21}H_{28}O_3$) C, H.

1,1-Ethylenedioxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane (31). To a stirred solution of compound **30** (40.05 g, 122.1 mmol) in distilled methanol (400 mL) in a 1 L three-neck round-bottom flask was added cerium chloride heptahydrate (45.5 g, 122.12 mmol). The reaction mixture was stirred for 35 min during which the salt progressively dissolved. The medium was cooled to 9 °C, and sodium borohydride (4.65 g, 123 mmol) was slowly added portionwise in 55 min. After the addition, the flask walls were rinsed with methanol (70 mL) and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The medium was cooled with an ice bath and hydrolyzed until neutral pH with 2 N HCl, and brine (100 mL) was added. The water layer was extracted with diethyl ether and the combined organic layers washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent the title compound **31** (40.12 g, 121.5 mmol) was obtained as a slightly colored oil in 99.5% yield and could be used as such in the following step: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.54 (ABXY, J = 15.4 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.41 (ABXY, J = 15.7 Hz and J = 7.0 Hz, 1H, $H_{2''}$), 4.01 (q, J = 6.5 Hz, 1H, $H_{3''}$), 3.93 and 3.95 (s, 4H, H_1 and H_2), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.27 (m, 1H, $H_{3'}$), 1.74 (m, 1H, $H_{2'e}$), 1.73 (m, 1H, $H_{5'e}$), 1.72 (m, 1H, $H_{6'e}$), 1.70 (m, 1H, $H_{4'e}$), 1.62 (m, 2H, $H_{6''}$), 1.50 (m, 2H, $H_{4''}$), 1.50 (m, 1H, $H_{5'a}$), 1.41 (m 1H, $H_{6'a}$), 1.35 (m, 2H, $H_{5''}$), 1.30 (t, J = 12.6 Hz, 1H, $H_{2'a}$), 1.0 (q, J = 12.5 Hz, 1H, $H_{4'a}$); IR (film) 3440, 1660, 960; MS (FAB$^+$) *m*/*z* 313 (M + H^+ − H_2O). Anal. ($C_{21}H_{30}O_3$) C, H.

3-[(*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl]cyclohexanone (32). To a stirred solution of silica gel (30 g) and a 15 wt % solution of sulfuric acid (1.5 g) in dichloromethane (50 mL) in a 250 mL three-neck round-bottom flask cooled with an ice bath was added dropwise a solution of compound **31** (8.22 g, 24.9 mmol) in dichloromethane (35 mL). After the reaction mixture was stirred for 16 h at room temperature, sodium hydrogen carbonate was added and stirring was continued for 3 h. After filtration, silica gel was washed with dichloromethane and the filtrate was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue (6.42 g) obtained as a yellow oil was purified on silica gel. Elution with cyclohexane/diethyl ether (65/35) afforded the title compound **32** (5.508 g, 19.25 mmol) in 77.5% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.57 (ABXY, 1H, J = 15.5 Hz and J = 6.5 Hz, $H_{1''}$), 5.44 (ABXY, 1H, J = 15.5 Hz and J = 6.2 Hz, $H_{2''}$), 4.03 (q, 1H, J = 6.4 Hz, $H_{3''}$), 2.59 (t, 2H, J = 7.6 Hz, $H_{7''}$), 2.45 (m, 1H, $H_{3'}$), 2.41 (m, 1H, $H_{2'e}$), 2.36 (m, 1H, $H_{6'e}$), 2.25 (m, 1H, $H_{6'a}$), 2.16 (m, 1H, $H_{2'a}$), 2.03 (m, 1H, $H_{5'e}$), 1.88 (m, 1H, $H_{4'e}$), 1.67 (m, 1H, $H_{5'a}$), 1.63 (m, 2H, $H_{6''}$), 1.52 (m, 2H, $H_{4''}$), 1.45 (m, 1H, $H_{4'a}$), 1.36 (m, 2H, $H_{5''}$); IR (film) 3320,

1690, 960; MS (FAB$^+$) *m/z* 269 (M − H_2O + H^+). Anal. ($C_{19}H_{26}O_2$) C, H.

1,1-Ethylenedioxy-3-[(*E*)-3-oxo-undec-1-en-1-yl]cyclohexane (33). Compound **33** was prepared from diethyl-2-oxodecylphosphonate **27** according to the procedure described for **30**. Purification by column chromatography (eluent: cyclohexane/diethyl ether, 80/20) afforded the title compound **30** in 70% yield: ^{1}H NMR (60 MHz, CCl_4) δ 6.62 (ABX, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1'}$), 5.95 (ABX, J = 15.5 Hz, 1H, $H_{2''}$), 3.86 (s, 4H, H_1 and H_2), 2.8−2.1 (m, 3H, $H_{3'}$ and $H_{4''}$), 2−1.05 (m, 20H, $H_{2'}$, $H_{4''}$-$H_{6'}$, $H_{5''}$-$H_{10''}$), 1.05−0.65 (m, 3H, $H_{11''}$); IR (film) 1680, 1620, 970; MS (IE, 20 eV) *m/z* 308 (M). Anal. ($C_{19}H_{32}O_3$) C, H, O.

1,1-Ethylenedioxy-3-[(*E*)-3-hydroxy-undec-1-en-1-yl]-cyclohexane (34). Compound **34** was prepared from **33** according to the procedure described for **31** (92% yield): ^{1}H NMR (60 MHz, CCl_4) δ 5.43 (m, 2H, $H_{1''}$ and $H_{2''}$), 4.13−3.82 (m, 1H, $H_{3''}$), 3.86 (s, 4H, H_1 and H_2), 2.7−1.05 (m, 24H, $H_{2'}$-$H_{6'}$, $H_{4''}$-$H_{10''}$ and OH), 1.05−0.65 (m, 3H, $H_{11''}$); IR (film) 3440, 1660, 960; MS (IE, 20 eV) *m/z* 292 (M − H_2O, 14). Anal. ($C_{19}H_{34}O_3$) C, H, O.

3-[(*E*)-3-Hydroxy-undec-1-en-1-yl]cyclohexanone (35). Compound **35** was prepared from **34** according to the procedure described for the preparation of **32**. Purification by column chromatography (eluent: cyclohexane/diethyl ether, 70/30) afforded the title compound **35** in 76.5% yield: ^{1}H NMR (60 MHz, CCl_4) δ 5.53 (m, 2H, $H_{1''}$ and $H_{2''}$), 4.15−3.8 (m, 1H, $H_{3''}$), 2.8−1.1 (m, 24H, $H_{2'}$-$H_{6'}$, $H_{4''}$-$H_{10''}$ and OH), 1.1−0.65 (m, 3H, $H_{11''}$); IR (film) 3400, 1695, 955; MS (IE, 20 eV) *m/z* 248 (M − H_2O). Anal. ($C_{17}H_{30}O_2$) C, H, O.

3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-undec-1-en-1-yl]cyclohexanone (36). Compound **36** was prepared from **35** according to the procedure described for **24 f**rom **32**. Purification by column chromatography (eluent: cyclohexane/diethyl ether, 98.5/1.5) afforded the title compound **36** in 89% yield: ^{1}H NMR (60 MHz, CCl_4) δ 5.42 (m, 2H, $H_{1''}$ and $H_{2''}$), 4.3−3.8 (m, 1H, $H_{3''}$), 2.7−1.05 (m, 9H, $H_{2'}$-$H_{6'}$), 1.2 (m, 14H, $H_{4''}$-$H_{10''}$), 0.9 (m, 12H, Si-*t*-Bu and $H_{11''}$), 0.0 (m, 6H, Si-CH_3); IR (film) 1705, 960, 825; MS (IE, 20 eV) *m/z* 323 (M − *t*-Bu). Anal. ($C_{23}H_{44}O_2Si$) C, H, O.

Ethyl 1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-undec-1-en-1-yl]-1-cyclohexane Acetate (37). Compound **37** was prepared from **36** according to the procedure described for **25**. Elution on silica gel afforded isomers **37ab** (cyclohexane/diethyl ether: 97/3) and **37cd** (cyclohexane/diethyl ether: 96/4) in 42.5% and 44% yield, respectively.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-undec-1-en-1-yl]-1-cyclohexane Acetate (37ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.38 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.31 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.16 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.96 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.37 (m, 1H, OH), 2.41 (m, 1H, $H_{3'}$), 2.4 (s, 2H, H_2), 1.8−1.11 (m, 23H, CH_3, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{10''}$), 1.03 (m, 2H, $H_{2'}$), 0.84 (m, 12H, Si-*t*-Bu and $H_{11''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 3460, 1710, 960; MS (IE, 20 eV) *m/z* = 411 (M − *t*-Bu). Anal. ($C_{27}H_{52}O_4Si$) C, H, O.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-undec-1-en-1-yl]-1-cyclohexane Acetate (37cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.40 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.32 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.97 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.83 (m, 1H, OH), 2.57 (m, 2H, H_2), 2.02 (m, 1H, $H_{3'}$), 1.8−1.1 (m, 23H, CH_3, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{10''}$), 1.02 (m, 2H, $H_{2'}$), 0.85 (m, 12H, *t*-Bu and $H_{11''}$), 0.0 (d, 6H, Si-CH_3); IR (film) 3460, 1710, 960; MS (IE, 20 eV) *m/z* = 319 (M − OTBDMS − H_2O). Anal. ($C_{27}H_{52}O_4Si$) C, H, O.

1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (38). Compound **38** was prepared by condensation of *N*,*N*-dimethylacetamide on **24** according to the procedure described for **25**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 65/35) to afford a first separation of the two isomers **38ab** and **38cd** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 83/17, 15 mL/min; **38ab**: 36 min; and **38cd**: 46 min). After HPLC chromatography, compounds **38ab** and **38cd** were isolated in, respectively, 50% and 32% yield.

(1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (38ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.23 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.40 (ABXY, 1H, J = 15.5 Hz and J = 6.5 Hz, $H_{1''}$), 5.33 (ABXY, 1H, J = 15.5 Hz and J = 6.8 Hz, $H_{2''}$), 5.14 (s, 1H, OH), 3.97 (q, 1H, J = 6.4 Hz, $H_{3''}$), 2.96 (s, 3H, N-CH_3), 2.92 (s, 3H, N-CH_3), 2.58 (t, 2H, J = 7.6 Hz, $H_{7''}$), 2.45 (m, 1H, $H_{3'}$), 2.33 (s, 2H, H_2), 1.83 (d, 1H, J = 15.3 Hz, $H_{2'e}$), 1.79 (d, 1H, J = 15.3 Hz, $H_{6'e}$), 1.76 (q, 1H, J = 14.9 Hz, $H_{5'a}$), 1.71 (d, 1H, J = 15.3 Hz, $H_{4'e}$), 1.58 (quint, 2H, J = 7.5 Hz, $H_{6''}$), 1.53 (d, 1H, J = 16.3 Hz, $H_{5'e}$), 1.41 (m, 2H, $H_{4''}$), 1.33 (m, 2H, $H_{5''}$), 1.09 (td, 1H, J = 13.8 Hz and J = 4.0 Hz, $H_{6'a}$), 0.94 (t, 1H, J = 12.6 Hz, $H_{2'a}$), 0.93 (qd, 1H, J = 14.9 Hz and J = 3.2 Hz, $H_{4'a}$), 0.86 (s, 9H, Si-*t*-Bu), −0.01 and 0.00 (s, 6H, Si-CH_3); IR (film) 3430, 1620, 1145. Anal. ($C_{29}H_{49}NO_3Si$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (38cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.69 (d, 1H, J = 5.0 Hz, OH), 5.40 (ABXY, 1H, J = 15.4 Hz and J = 6.1 Hz, $H_{1''}$), 5.32 (ABXY, 1H, J = 6.1 Hz and J = 15.4 Hz, $H_{2''}$), 3.97 (q, 1H, J = 6.1 Hz, $H_{3''}$), 3.02 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.57 (t, 2H, J = 7.2 Hz, $H_{7''}$), 2.51 (m, 2H, H_2), 1.96 (m, 1H, $H_{3'}$), 1.84 (m, 2H, $H_{6'e}$ and $H_{2'e}$), 1.70 (m, 1H, $H_{5'e}$), 1.65 (m, 1H, $H_{4'e}$), 1.58 (quint, 2H, J = 7.5 Hz, $H_{6''}$), 1.43 (m, 2H, $H_{4''}$), 1.37 (m, 1H, $H_{6'a}$), 1.29 (m, 3H, $H_{5''}$ and $H_{5'a}$), 1.27 (m, 1H, $H_{2'a}$), 1.01 (m, 1H, $H_{4'a}$), 0.85 (m, 9H, Si-*t*-Bu), 0.01 (m, 6H, Si-CH_3); IR (film) 3430, 1620, 1145. Anal. ($C_{29}H_{49}NO_3Si$) C, H, N, O.

1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*-methyl-*N*-phenyl-acetamide (39). Compound **39** was prepared by condensation of *N*-methyl-*N*-phenylacetamide on **24** according to the procedure described for **25**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 88/12) to afford a first separation of the two isomers **39ab** and **39cd** which were further purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/diethyl ether: 60/40, 9 mL/min; **39ab**: 23 min; and **39cd**: 34 min). After HPLC chromatography, compounds **39ab** and **39cd** were isolated in, respectively, 45% and 34% yield.

(1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*-methyl-*N*-phenyl-acetamide (39ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44 (m, 2H, H_4), 7.36 (m, 1H, H_6), 7.22 (m, 2H, $H_{10''}$), 7.14 (m, 5H, $H_{9''}$, $H_{11''}$ and H_5), 5.36 (ABXY, J = 15.6 Hz and J = 6.4 Hz, 1H, $H_{1''}$), 5.30 (ABXY, J = 15.6 Hz and J = 6.9 Hz, 1H, $H_{2''}$), 5.14 (s, 1H, OH), 3.97 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.26 (s, 3H, N-CH_3), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.43 (m, 1H, $H_{3'}$), 2.12 (s, 2H, H_2), 1.75 (d, J = 14.1 Hz, 1H, $H_{2'e}$), 1.75 (q, J = 15.1 Hz, 1H, $H_{5'a}$), 1.70 (d, J = 15.8 Hz, 1H, $H_{6'e}$), 1.68 (d, J = 16.8 Hz, 1H, $H_{4'e}$), 1.61 (quint, J = 8.4 Hz, 2H, $H_{6''}$), 1.50 (d, J = 15.1 Hz, 1H, $H_{5'e}$), 1.46 (m, 2H, $H_{4''}$), 1.32 (m, 2H, $H_{5''}$), 0.91 (td, J = 16.0 Hz and J = 4.2 Hz, 1H, $H_{6'a}$), 0.87 (s, 9H, Si-*t*-Bu), 0.85 (qd, J = 14.6 Hz and J = 3.1 Hz, 1H, $H_{4'a}$), 0.77 (t, J = 14.3 Hz, 1H, $H_{2'a}$), −0.01 and 0.00 (s, 6H, Si-CH_3); IR (film) 3400, 1625, 1110, 960. Anal. ($C_{34}H_{51}NO_3Si$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*-methyl-*N*-phenyl-acetamide (39cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44 (m, 2H, H_4), 7.36 (m, 1H, H_6), 7.22 (m, 2H, $H_{10''}$), 7.14 (m, 5H, $H_{9''}$, $H_{11''}$ and H_5), 5.97 (d, 1H, OH), 5.40 (ABXY, 1H, J = 15.4 Hz and J = 6.3 Hz, $H_{1''}$), 5.32 (ABXY, 1H, J = 15.4 Hz and J = 6.7 Hz, $H_{2''}$), 3.97 (q, 1H, J = 6.7 Hz, $H_{3''}$), 3.26 (s, 3H, N-CH_3), 2.57 (t, 2H, J = 7.2 Hz, $H_{7''}$), 2.26 and 2.32 (AB, 2H, J = 15.8 Hz, H_2), 1.90 (m, 1H, $H_{3'}$), 1.82 (m, 1H, $H_{2'e}$), 1.81 (m, 1H, $H_{6'e}$), 1.72 (m, 1H, $H_{5'e}$), 1.66 (m, 1H, $H_{4'e}$), 1.57 (m, 2H, $H_{6''}$), 1.44 (m, 2H, $H_{4''}$), 1.37 (m, 1H, $H_{6'a}$), 1.31 (m, 2H, $H_{5''}$), 1.26 (m, 1H, $H_{2'a}$), 1.22 (m, 1H, $H_{5'a}$), 1.00 (m, 1H, $H_{4'a}$), 0.83 (s, 9H,

Si-*t*-Bu), 0.00 and 0.02 (s, 6H, Si-CH_3); IR (film) 3400, 1625, 1110, 960. Anal. ($C_{34}H_{51}NO_3Si$) C, H, N, O.

1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dipropyl-acetamide (40). Compound **40** was prepared by condensation of *N*,*N*-dipropylacetamide on **24** according to the procedure described for **25**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 90/10) to afford a first separation of the two isomers **40ab** and **40cd** which were further purified by preparative HPLC (10 μm Nucleosil, 10 × 250 mm, cyclohexane/diethyl ether: 85/15, 4 mL/min; **40ab**: 21 min; and **40cd**: 29 min). After HPLC chromatography, compounds **40ab** and **40cd** were isolated in, respectively, 50% and 34.5% yield.

(1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dipropyl-acetamide (40ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.41 (m, 1H, $H_{1''}$), 5.38 (s, 1H, OH), 5.32 (m, 1H, $H_{2''}$), 3.96 (q, J = 5.8 Hz, 1H, $H_{3''}$), 3.27 (q, J = 9.7 Hz and J = 7.2 Hz, 2H, H_6), 3.16 (t, J = 7.6 Hz, 2H, H_3), 2.57 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.45 (m, 1H, $H_{3'}$), 2.33 (s, 2H, H_2), 1.79 (d, J = 15.0 Hz, 1H, $H_{2'e}$), 1.77 (m, 1H, $H_{5'a}$), 1.76 (d, J = 13.5 Hz, 1H, $H_{6'e}$), 1.71 (m, 1H, $H_{4'e}$), 1.57 (m, 2H, H_4), 1.57 (m, 2H, $H_{6''}$), 1.55 (m, 2H, H_7), 1.52 (m, 1H, $H_{5'e}$), 1.43 (m, 2H, $H_{4''}$), 1.31 (m, 2H, $H_{5''}$), 1.08 (td, J = 13.5 Hz and J = 4.3 Hz, 1H, $H_{6'a}$), 0.91 (t, 1H, $H_{2'a}$), 0.91 (m, 3H, H_5), 0.89 (m, 1H, $H_{4'a}$), 0.85 (m, 3H, H_8), 0.84 (s, 9H, Si-*t*-Bu), 0.00 and 0.02 (s, 6H, Si-CH_3); IR (film) 3380, 1605, 1120, 960. Anal. ($C_{33}H_{57}NO_3Si$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-*tert*-butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dipropyl-acetamide (40cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$, $H_{11''}$), 5.97 (d, 1H, OH), 5.40 (ABXY, 1H, J = 15.4 Hz and J = 6.3 Hz, $H_{1''}$), 5.32 (ABXY, 1H, J = 15.4 Hz and J = 6.7 Hz, $H_{2''}$), 3.97 (q, 1H, J = 6.7 Hz, $H_{3''}$), 3.31 and 3.22 (m, 2H, H_6), 3.20 (m, 2H, H_3), 2.57 (t, 2H, J = 7.2 Hz, $H_{7''}$), 2.47 and 2.54 (AB, 2H, J = 15.8 Hz, H_2), 1.90 (m, 1H, $H_{3'}$), 1.82 (m, 1H, $H_{2'e}$), 1.81 (m, 1H, $H_{6'e}$), 1.72 (m, 1H, $H_{5'e}$), 1.66 (m, 1H, $H_{4'e}$), 1.57 (m, 2H, $H_{6''}$), 1.56 (m, 2H, H_4), 1.52 (m, 2H, H_7), 1.44 (m, 2H, $H_{4''}$), 1.37 (m, 1H, $H_{6'a}$), 1.31 (m, 2H, $H_{5''}$), 1.26 (m, 1H, $H_{2'a}$), 1.22 (m, 1H, $H_{5'a}$), 1.00 (m, 1H, $H_{4'a}$), 0.93 (t, 3H, J = 7.6 Hz, H_5), 0.86 (m, 3H, H_8), 0.83 (s, 9H, Si-*t*-Bu), 0.00 and 0.02 (s, 6H, Si-CH_3); IR (film) 3380, 1605, 1120, 960. Anal. ($C_{33}H_{57}NO_3Si$) C, H, N, O.

Methyl 3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexylidene Acetate (41). To a stirred solution of sodium hydride 60% dispersion in mineral oil (0.259 g, 6.48 mmol) in freshly distilled THF (25 mL) under nitrogen in a 100 mL three-neck round-bottom flask equipped with a dropping funnel, a condenser, and a thermometer was added dropwise a solution of diethyl methylphosphonoacetate (1.430 g, 6.80 mmol) in dry THF (10 mL). The reaction mixture was stirred for 30 min at room temperature, and a solution of compound **24** (1.300 g, 3.24 mmol) in dry THF (10 mL) was added dropwise in 30 min. The colorless solution became yellow. The reaction was heated at 60 °C for 1 h and became orange. The medium was cooled with an ice bath, hydrolyzed with ice cold water (30 mL), and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oily residue (1.607 g) which was chromatographed on silica gel. Elution of cyclohexane/diethyl ether (98/2) afforded a first separation of the two isomers **41ab** and **41cd** which were further purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/diethyl ether: 98/2, 5 mL/min; **41ab**: 39 min; and **41cd**: 42 min 30 s). After HPLC chromatography, compounds **41ab** (0.428 g, 0.94 mmol) and **41cd** (0.919 g, 2.01 mmol) were isolated in, respectively, 29% and 62% yield.

Methyl (*Z*)-3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexylidene Acetate (41ab): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.64 (s, 1H, H_2), 5.50 (ABXY, J = 15.4 Hz and J = 5.6 Hz, 1H, $H_{1''}$), 5.41 (ABXY, J = 6.4 Hz and J = 15.4 Hz, 1H, $H_{2''}$), 4.01 (q, J = 6.0 Hz, 1H, $H_{3''}$), 3.67 (m, 1H, $H_{2'e}$), 3.67 (s, 3H, OMe), 2.60 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.25 (d, J = 12.7 Hz, 1H, $H_{6'e}$), 2.17 (m, 1H, $H_{3'}$), 2.11 (td, J = 12.7 Hz and J = 4.6 Hz, 1H, $H_{6'a}$), 1.91 (m, 1H, $H_{5'e}$), 1.90 (m, 1H, $H_{2'a}$), 1.82 (m, 1H, $H_{4'e}$), 1.62 (m, 2H, $H_{6''}$), 1.50 (m, 2H, $H_{4''}$), 1.47 (m, 1H, $H_{5'a}$), 1.38 (m, 2H, $H_{5''}$), 1.32 (m, 1H, $H_{4'a}$), 0.88 (s, 9H, Si-*t*-Bu), 0.02 (s, 6H, Si-CH_3); IR (film) 1710, 1640, 960. Anal. ($C_{28}H_{44}O_3Si$) C, H, O.

Methyl (*E*)-3-[(*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl]cyclohexylidene Acetate (41cd): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.62 (s, 1H, H_2), 5.44 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.36 (ABXY, J = 6.5 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 4.00 (q, J = 6.0 Hz, 1H, $H_{3''}$), 3.67 (s, 3H, OMe), 3.62 (d, J = 13.7 Hz, 1H, $H_{6'e}$), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.26 (m, 1H, $H_{2'e}$), 2.15 (m, 1H, $H_{3'}$), 1.99 (m, 1H, $H_{6'a}$), 1.97 (m, 1H, $H_{2'a}$), 1.89 (m, 1H, $H_{5'e}$), 1.79 (m, 1H, $H_{4'e}$), 1.60 (quint, J = 7.5 Hz, 2H, $H_{6''}$), 1.49 (m, 2H, $H_{4''}$), 1.42 (m, 1H, $H_{5'a}$), 1.35 (m, 2H, $H_{5''}$), 1.29 (m, 1H, $H_{4'a}$), 0.87 (s, 9H, Si-*t*-Bu), 0.01 (s, 6H, Si-CH_3); IR (film) 1710, 1640, 960; MS (FAB$^+$) *m*/*z* 399 (M − *t*-Bu). Anal. ($C_{28}H_{44}O_3Si$) C, H, O.

[3-((*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (42). Compound **42** was prepared by condensation of diethyl *N*,*N*-dimethylacetamidephosphonate to **24** according to the procedure described for **41**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 55/45) to afford a first separation of the two isomers **42ab** and **42cd** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 85/15, 15 mL/min; **42ab**: 30 min; and **42cd**: 44 min). After HPLC chromatography, compounds **42ab** and **42cd** were isolated in, respectively, 33.5% and 52.5% yield.

[(*Z*)-3-((*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (42ab): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.72 (s, 1H, H_2), 5.46 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.35 (ABXY, J = 6.8 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 3.98 (q, J = 6.0 Hz, 1H, $H_{3''}$), 3.00 (s, 3H, N-CH_3), 2.95 (s, 3H, N-CH_3), 2.88 (d, J = 10.8 Hz, 1H, $H_{2'e}$), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.22 (m, J = 12.7 Hz, 1H, $H_{6'e}$), 2.09 (m, 1H, $H_{3'}$), 2.04 (td, J = 12.7 Hz and J = 4.6 Hz, 1H, $H_{6'a}$), 1.86 (m, 1H, $H_{5'e}$), 1.77 (m, 1H, $H_{4'e}$), 1.73 (t, J = 10.8 Hz, 1H, $H_{2'a}$), 1.58 (m, 2H, $H_{6''}$), 1.44 (m, 2H, $H_{4''}$), 1.41 (m, 1H, $H_{5'a}$), 1.31 (m, 2H, $H_{5''}$), 1.22 (m, 1H, $H_{4'a}$), 0.85 (s, 9H, Si-*t*-Bu), 0.00 (s, 6H, Si-CH_3); IR (film) 1640, 1630, 1135, 960; MS (FAB$^+$) *m*/*z* 338 (M − OTBDMS). Anal. ($C_{29}H_{47}NO_2Si$) C, H, N, O.

[(*E*)-3-((*E*)-3-*tert*-Butyldimethylsilyloxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (42cd): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.72 (s, 1H, H_2), 5.45 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.35 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{2''}$), 3.98 (q, J = 6.0 Hz, 1H, $H_{3''}$), 3.00 (s, 3H, N-CH_3), 2.95 (s, 3H, N-CH_3), 2.86 (d, J = 12.6 Hz, 1H, $H_{6'e}$), 2.58 (t, J = 7.2 Hz, 2H, $H_{7''}$), 2.23 (mt, J = 12.6 Hz, 1H, $H_{2'e}$), 2.11 (m, 1H, $H_{3'}$), 1.91 (mt, J = 12.6 Hz, 1H, $H_{2'a}$), 1.86 (m, 1H, $H_{6'a}$), 1.82 (m, 1H, $H_{5'e}$), 1.74 (m, 1H, $H_{4'e}$), 1.59 (quint, J = 7.6 Hz, 2H, $H_{6''}$), 1.46 (m, 2H, $H_{4''}$), 1.38 (m, 1H, $H_{5'a}$), 1.32 (m, 2H, $H_{5''}$), 1.22 (m, 1H, $H_{4'a}$), 0.86 (s, 9H, Si-*t*-Bu), 0.00 (s, 6H, Si-CH_3); IR (film) 1640, 1630, 1135, 960; MS (FAB$^+$) *m*/*z* 338 (M − OTBDMS). Anal. ($C_{29}H_{47}NO_2Si$) C, H, N, O.

3-[(*E*)-3-Oxo-7-phenyl-1-hepten-1-yl]cyclohexanone (44). To a stirred solution of compound **30** (1.50 g, 4.57 mmol) in acetone/water: 95/5 (40 mL) was added portionwise pyridinium *p*-toluenesulfonate (344 mg, 1.37 mmol). The reaction mixture was refluxed for 4 h, and the solvent was evaporated under reduced pressure. The resulting residue was taken up with diethyl ether, washed with saturated $NaHCO_3$ and with brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue (1.320 g) obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 80/20) to afford the title compound **44** as a colorless oil in 96% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 6.70 (ABX,

J = 15.9 Hz and J = 6.6 Hz, 1H, $H_{1''}$), 6.06 (ABX, J = 15.9 Hz and J = 1.2 Hz, 1H, $H_{2''}$), 2.63 (m, 1H, $H_{3'}$), 2.61 (t, J = 7.0 Hz, 2H, $H_{7''}$), 2.53 (t, J = 6.9 Hz, 2H, $H_{4''}$), 2.45 (d, J = 14.0 Hz, 1H, $H_{2'e}$), 2.39 (d, J = 14.6 Hz, 1H, $H_{6'e}$), 2.28 (td, J = 11.9 Hz and J = 6.0 Hz, 1H, $H_{6'a}$), 2.23 (t, J = 12.6 Hz, 1H, $H_{2'a}$), 2.06 (d, J = 14.6 Hz, 1H, $H_{5'e}$), 1.96 (d, J = 13.0 Hz, 1H, $H_{4'e}$), 1.72 (q, J = 15.1 Hz, 1H, $H_{5'a}$), 1.63 (quint, J = 3.6 Hz, 2H, $H_{5''}$), 1.63 (quint, J = 3.6 Hz, 2H, $H_{6''}$), 1.56 (qd, J = 11.6 Hz and J = 3.7 Hz, 1H, $H_{4'a}$); IR (film) 1705, 1665, 1625, 970; MS (FAB^+) m/z 285 ($M + H^+$). Anal. ($C_{19}H_{24}O_2$) C, H, O.

1,1-Ethylenedioxy-3-[(*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane (45). To a stirred solution of compound **30** (992 mg, 3.020 mmol) in dry diethyl ether (50 mL) under nitrogen in a 100 mL round-bottom flask was added dropwise at −35 °C a 1.56 M solution of methyllithium (3.72 mL, 5.803 mmol) in diethyl ether. The reaction was exothermic, and the mixture became yellow. The reaction mixture was allowed to warm to room temperature for 1 h. The medium was hydrolyzed with ice cold water, and stirring was continued for 20 min. The water layer was extracted with diethyl ether (2 × 50 mL), and the combined organic layers were washed with brine (2 × 10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue (1.103 g) obtained as a yellow oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 85/15) to afford the title compound **45** (976 mg, 2.833 mmol) as a colorless oil in 94% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.52 (ABX, J = 15.8 Hz and J = 5.8 Hz, 1H, $H_{1''}$), 5.45 (AB, J = 15.8 Hz, 1H, $H_{2''}$), 3.93 (s, 4H, H_1 and H_2), 2.59 (t, J = 7.5 Hz, 2H, $H_{7''}$), 2.26 (m, 1H, $H_{3'}$), 1.75 (d, J = 12.6 Hz, 1H, $H_{2'e}$), 1.73 (m, 1H, $H_{5'e}$), 1.72 (m, 1H, $H_{6'e}$), 1.68 (m, 1H, $H_{4'e}$), 1.60 (m, 2H, $H_{6''}$), 1.57 (m, 1H, $H_{5'a}$), 1.52 (m, 2H, $H_{4''}$), 1.41 (td, J = 13.3 Hz and J = 4.7 Hz, 1H, $H_{6'a}$), 1.34 (m, 2H, $H_{5''}$), 1.30 (t, J = 12.6 Hz, 1H, $H_{2'a}$), 1.22 (s, 3H, CH_3), 0.99 (qd, J = 12.2 Hz and J = 3.6 Hz, 1H, $H_{4'a}$); IR (film) 3460, 960; MS (FAB^+) m/z 327 ($M + H^+ - H_2O$). Anal. ($C_{22}H_{32}O_3$) C, H, O.

3-[(*E*)-3-Hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexanone (46). Compound **46** was prepared from **45** according to the procedure described for **44**. The residue was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 80/20) to afford a mixture of isomers **46** and **47** in, respectively, 58% and 14% yield (ratio 80:20 as determined by ^{1}H NMR). As these compounds could not be separated by HPLC, the mixture was submitted in the following step to silylation conditions which derivatized selectively compound **47**.

Compound **46**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.56 (ABX, J = 15.8 Hz and J = 5.8 Hz, 1H, $H_{1''}$), 5.47 (AB, J = 15.8 Hz, 1H, $H_{2''}$), 2.59 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.47 (m, 1H, $H_{3'}$), 2.40 (m, 1H, $H_{2'e}$), 2.35 (m, 1H, $H_{6'e}$), 2.25 (m, 1H, $H_{6'a}$), 2.18 (m, 1H, $H_{2'a}$), 2.04 (m, 1H, $H_{5'e}$), 1.88 (m, 1H, $H_{4'e}$), 1.68 (m, 1H, $H_{5'a}$), 1.60 (m, J = 7.6 Hz, 2H, $H_{6''}$), 1.52 (m, 2H, $H_{4''}$), 1.48 (m, 1H, $H_{4'a}$), 1.32 (m, 2H, $H_{5''}$), 1.23 (s, 3H, CH_3); IR (film) 3440, 1705, 960; MS (IE, 70 eV) m/z 282 ($M - H_2O$). Anal. ($C_{20}H_{28}O_2$) C, H, O.

3-(1-Hydroxy-3-methyl-7-phenylhept-2-en-1-yl)cyclohexanone (47): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.09 (d, J = 8.3 Hz, 1H, $H_{2''}$), 4.19 (dd, J = 5.0 Hz and J = 9.0 Hz, 1H, $H_{1''}$), 2.60 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.46 (d, J = 14.4 Hz, 1H, $H_{2'e}$), 2.33 (d, J = 14.4 Hz, 1H, $H_{6'e}$), 2.19 (td, J = 14.4 Hz and J = 7.2 Hz, 1H, $H_{6'a}$), 2.14 (t, J = 14.4 Hz, 1H, $H_{2'a}$), 2.04 (d, J = 16.9 Hz, 1H, $H_{5'e}$), 2.01 (t, J = 7.2 Hz, 2H, $H_{4''}$), 1.79 (d, J = 15.9 Hz, 1H, $H_{4'e}$), 1.78 (m, 1H, $H_{3'}$), 1.60 (quint, J = 10.8 Hz, 2H, $H_{6''}$), 1.57 (m, 1H, $H_{5'a}$), 1.44 (qd, J = 10.8 Hz and J = 3.6 Hz, 1H, $H_{4'a}$), 1.42 (quint, J = 7.2 Hz, 2H, $H_{5''}$); IR (film) 3410, 1690, 1650. Anal. ($C_{20}H_{28}O_2$) C, H, O.

3-[(*E*)-1-*tert*-Butyldimethylsilyloxy-3-methyl-7-phenylhept-2-en-1-yl]cyclohexanone (48). The mixture of compounds **46** and **47** was submitted to silylation conditions (procedure described for **24** from **32**) in order to derivatize selectively compound **47** which could then be easily separated from the unchanged **46**. The residue was purified by column chromatography on silica gel to afford successively compounds **48** (eluent: cyclohexane/diethyl ether, 95/5) and **46** (eluent: cyclohexane/diethyl ether, 50/50) in quantitative yields: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.09 (d, J = 8.3 Hz, 1H, $H_{2''}$), 4.19 (dd, J = 5.0 Hz and J = 9.0 Hz, 1H, $H_{1''}$), 2.60 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.46 (d, J = 14.4 Hz, 1H, $H_{2'e}$), 2.33 (d, J = 14.4 Hz, 1H, $H_{6'e}$), 2.19 (td, J = 14.4 Hz and J = 7.2 Hz, 1H, $H_{6'a}$), 2.14 (t, J = 14.4 Hz, 1H, $H_{2'a}$), 2.04 (d, J = 16.9 Hz, 1H, $H_{5'e}$), 2.01 (t, J = 7.2 Hz, 2H, $H_{4''}$), 1.79 (d, J = 15.9 Hz, 1H, $H_{4'e}$), 1.78 (m, 1H, $H_{3'}$), 1.60 (quint, J = 10.8 Hz, 2H, $H_{6''}$), 1.57 (m, 1H, $H_{5'a}$), 1.44 (qd, J = 10.8 Hz and J = 3.6 Hz, 1H, $H_{4'a}$), 1.42 (quint, J = 7.2 Hz, 2H, $H_{5''}$), 0.86 (s, 9H, Si-*t*-Bu), −0.04 and 0.00 (s, 6H, Si-CH_3); IR (film) 3410, 1690, 1650. Anal. ($C_{26}H_{42}O_2Si$) C, H, O.

3-[(*E*)-3-Fluoro-7-phenyl-1-hepten-1-yl]cyclohexanone (49). To a stirred solution of compound **32** (100 mg, 0.349 mmol) in dry freshly distilled dichloromethane (2.5 mL) was added under nitrogen at −80 °C morpholinosulfurtrifluoride (50 μL, 0.410 mmol). The reaction mixture was stirred for 10 min at −75 °C and hydrolyzed with saturated NH_4Cl (2 mL). The resulting mixture was transferred to a separatory funnel containing ethyl acetate (40 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was washed with distilled water (2 × 10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue (102 mg) obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 90/10) to afford a mixture of isomers **49** and **50** in the ratio 68/32. Further preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 95/5, 15 mL/min; **50**: 18 min and **49**: 21 min) afforded the separation of compounds **49** (56 mg, 0.195 mmol) and **50** (26 mg, 0.090 mmol) which were isolated in, respectively, 56% and 26% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26 (m, 2H, $H_{10''}$), 7.16 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.67 (m, 1H, $H_{1''}$), 5.49 (m, 1H, $H_{2''}$), 4.80 (qd, J = 48.7 Hz and J = 6.4 Hz, 1H, $H_{3''}$), 2.61 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.50 (m, 1H, $H_{3'}$), 2.43 (m, 1H, $H_{2'e}$), 2.36 (d, J = 15.2 Hz, 1H, $H_{6'e}$), 2.28 (t, J = 11.8 Hz, 1H, $H_{6'a}$), 2.17 (t, J = 13.5 Hz, 1H, $H_{2'a}$), 2.05 (m, 1H, $H_{5'e}$), 1.92 (m, 1H, $H_{4'e}$), 1.68 (q, J = 15.2 Hz, 1H, $H_{5'a}$), 1.67 (m, 2H, $H_{4''}$), 1.64 (quint, J = 7.8 Hz, 2H, $H_{6''}$), 1.49 (q, J = 14.1 Hz, 1H, $H_{4'a}$), 1.41 (m, 2H, $H_{5''}$); ^{19}F NMR (235 MHz, $CDCl_3$) δ −172.7 (m); IR (film) 1705, 960; MS (FAB^+) m/z 269 ($M - HF + H^+$). Anal. ($C_{19}H_{25}OF$) C, H, O.

3-[(*E*)-1-Fluoro-7-phenylhept-2-en-1-yl]cyclohexanone (50): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.26 (m, 2H, $H_{10''}$), 7.16 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.75 (m, 1H, $H_{3''}$), 5.46 (m, 1H, $H_{2''}$), 4.67 and 4.61 (td, J = 48.1 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 2.60 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.38 (d, J = 15.9 Hz, 1H, $H_{6'e}$), 2.34 (d, J = 15.9 Hz, 1H, $H_{2'e}$), 2.26 (t, J = 13.5 Hz, 1H, $H_{6'a}$), 2.14 (t, J = 13.5 Hz, 1H, $H_{2'a}$), 2.11 (d, J = 17.5 Hz, 1H, $H_{5'e}$), 2.10 (m, 2H, $H_{4''}$), 2.06 (m, 1H, $H_{3'}$), 2.04 (d, J = 17.5 Hz, 1H, $H_{4'e}$), 1.63 (quint, J = 8.3 Hz, 2H, $H_{6''}$), 1.63 (q, J = 14.7 Hz, 1H, $H_{5'a}$), 1.46 (q, J = 13.7 Hz, 1H, $H_{4'a}$), 1.44 (quint, J = 7.9 Hz, 2H, $H_{5''}$); ^{19}F NMR (235 MHz, $CDCl_3$) δ −177.1 (md, J = 48.0 Hz), −179.7 (md, J = 47.7 Hz); IR (film) 1705, 960; MS (FAB^+) m/z 269 ($M - HF + H^+$). Anal. ($C_{19}H_{25}OF$) C, H, O.

Methyl (1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-oct-1-en-1-yl]-4-cyclohexane Butanoate (1a) and Methyl (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-oct-1-en-1-yl]-4-cyclohexane Butanoate (1b).** To a stirred solution of lactone **20ab** (2 mmol) in distilled THF (25 mL) cooled to 0 °C was added 1 N HCl (4 mL, 4 mmol). The reaction mixture was stirred for 64 h at room temperature, and sodium hydrogencarbonate (0.336 g, 4 mmol) was added. The medium was concentrated and then taken up with 50 mL of diethyl ether. The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with distilled water (2 × 10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by chromatography. The hydroxy lactone obtained was treated with 2 equiv of triethylamine in methanol at room temperature for 3 days. After evaporation of the solvent the crude methyl ester was purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/ethyl acetate: 90/10, 10 mL/min; **1a**: 23 min and

1b: 27 min) which afforded isomers **1a** and **1b** in 43% and 42% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.50 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{1''}$), 5.38 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{2''}$), 4.00 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.65 (s, 3H, CH_3), 2.36 (m, 1H, $H_{3'}$), 2.28 (t, 2H, J = 7.1 Hz, H_2), 1.90−0.90 (m, 20H, H_3-H_4, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.86 (m, 3H, $H_{8''}$); IR (film) 3400, 1720, 1200, 960. Anal. ($C_{19}H_{34}O_4$) C, H, O.

Methyl (1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-oct-1-en-1-yl]-4-cyclohexane Butanoate (1c) and Methyl (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-oct-1-en-1-yl]-4-cyclohexane Butanoate (1d).** Compounds **1c** and **1d** were prepared from the lactone **20cd** according to the procedure described for **1a** and **1b**. Preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/ethyl acetate: 85/15, 10 mL/min; **1c**: 20 min and **1d**: 25 min) afforded isomers **1c** and **1d** in 41% and 40% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.48 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{1''}$), 5.36 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{2''}$), 3.96 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.63 (s, 3H, CH_3), 2.33 (t, 2H, J = 7.1 Hz, H_2), 2.05 (m, 1H, $H_{3'}$), 1.85−0.90 (m, 20H, H_3-H_4, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.86 (m, 3H, $H_{8''}$); IR (film) 3400, 1720, 1200, 960. Anal. ($C_{19}H_{34}O_4$) C, H, O.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-oct-1-en-1-yl]-1-cyclohexane Acetate (2a) and Ethyl (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-oct-1-en-1-yl]-1-cyclohexane Acetate (2b).** To a stirred solution of compound **21ab** (0.730 g, 1.710 mmol) in distilled THF (20 mL) cooled to 0 °C was added 1 N HCl (3.5 mL, 3.5 mmol). The reaction mixture was stirred for 64 h at room temperature, and sodium hydrogen carbonate (0.58 g, 7 mmol) was added. The medium was concentrated and then taken up with 50 mL of diethyl ether. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with distilled water (2 × 10 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 60/40) to afford a first separation of the two isomers **2a** and **2b**. Further preparative HPLC purification (10 μm Rsil, 22 × 250 mm, cyclohexane/diethyl ether: 80/20, 10 mL/min; **2a**: 23 min; and **2b**: 27 min) afforded isomers **2a** (0.229 g, 0.735 mmol) and **2b** (0.213 g, 0.684 mmol) in 43% and 40% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.52 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{1''}$), 5.40 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{2''}$), 4.17 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 4.00 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.45 (m, 1H, $H_{3'}$), 2.40 (s, 2H, H_2), 1.80−0.90 (m, 19H, CH_3, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.86 (m, 3H, $H_{8''}$); IR (film) 3400, 1710. Anal. ($C_{18}H_{32}O_4$) C, H, O.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-oct-1-en-1-yl]-1-cyclohexane acetate (2c)** and **Ethyl (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-oct-1-en-1-yl]-1-cyclohexane Acetate (2d).** Compounds **2c** and **2d** were prepared from **21cd** according to the procedure described for **2a** and **2b**. Preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/diethyl ether: 75/25, 10 mL/min; **2c**: 20 min; and **2d**: 25 min) afforded isomers **2c** and **2d** in 40% and 42% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.53 (ABXY, 1H, J = 15.5 Hz and J = 6.5 Hz, $H_{1''}$), 5.40 (ABXY, 1H, J = 15.5 Hz and J = 6.8 Hz, $H_{2''}$), 4.18 (q, J = 7.2 Hz, 2H, CH_2CH$_3$), 4.00 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.58 (s, 2H, H_2), 2.05 (m, 1H, $H_{3'}$), 1.80−0.90 (m, 19H, CH_3, $H_{2'}$, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{7''}$), 0.87 (m, 3H, $H_{8''}$); IR (film) 3400, 1715. Anal. ($C_{18}H_{32}O_4$) C, H, O.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (3a) and Ethyl (1*S**,3*S**)-1-Hydroxy-3-[(3 *R***S**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (3b).** Compounds **3a** and **3b** were prepared from **25ab** according to the procedure described for **2a** and **2b.** Preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 87.5/12.5, 20 mL/min; **3a**: 75 min; and **3b**: 85 min) afforded isomers **3a** and **3b** in 38% and 46% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.52 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{1''}$), 5.40 (ABXY, 1H, J = 14.4 Hz and J = 6.4 Hz, $H_{2''}$), 4.16 (q, 2H, J = 7.1 Hz, CH_2CH$_3$), 3.99 (q, 1H, J = 6.4 Hz, $H_{3''}$), 3.37 (s, 1H, OH), 2.58 (t, 2H, J = 7.5 Hz, $H_{7''}$), 2.42 (m, 1H, $H_{3'}$), 2.41 (s, 2H, H_2), 1.77 (d, 1H, J = 13.4 Hz, $H_{2'e}$), 1.73 (d, 1H, J = 14.4 Hz, $H_{5'a}$), 1.72 (d, 1H, J = 14.4 Hz, $H_{6'e}$), 1.71 (d, 1H, J = 12.6 Hz, $H_{4'e}$), 1.61 (quint, 2H, J = 7.8 Hz, $H_{6''}$), 1.55 (d, 1H, J = 11.9 Hz, $H_{5'e}$), 1.50 (m, 2H, $H_{4''}$), 1.37 (m, 2H, $H_{5''}$), 1.26 (t, 3H, J = 7.1 Hz, CH_3), 1.18 (td, 1H, J = 13.5 Hz and J = 4.0 Hz, $H_{6'a}$), 1.03 (t, 1H, J = 12.8 Hz, $H_{2'a}$), 0.95 (qd, 1H, J = 12.6 Hz and J = 4.0 Hz, $H_{4'a}$); IR (film) 3410, 1720, 1185, 960; UV λ_{max} (cyclohexane) 262 (ϵ = 224); MS (FAB$^+$) m/z = 339 (M − 2H_2O + H$^+$); HRMS (FAB$^+$, M + Na$^+$) 397.33670 (397.23548 calcd for $C_{23}H_{34}O_4Na$). Anal. ($C_{23}H_{34}O_4$) C, H, O.

Chiral HPLC separation (5 μm Chiralcel OD, 10.5 × 250 mm, heptane/2-propanol: 92.5/7.5, 1 mL/min, 34 °C; **3bα**: 15 min and **3b*β***: 24 min) from racemic diastereoisomer **3b** afforded enantiomers **3bα** ([α]$_D$ = −4.2°, $CHCl_3$) and **3b*β*** ([α]$_D$ = +4.2°, $CHCl_3$).

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (3c) and Ethyl (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (3d).** Compounds **3c** and **3d** were prepared from **25cd** according to the procedure described for **3a** and **3b**. The crude residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 60/40) to afford a first separation of the two isomers **3c** and **3d** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 80/20, 15 mL/min; **3c**: 42 min; and **3d**: 52 min). After HPLC chromatography, compounds **3c** and **3d** were isolated in, respectively, 39% and 37.5% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.53 (ABXY, 1H, J = 15.5 Hz and J = 6.5 Hz, $H_{1''}$), 5.40 (ABXY, 1H, J = 15.5 Hz and J = 6.8 Hz, $H_{2''}$), 4.17 (q, 2H, J = 7.2 Hz, CH_2CH$_3$), 4.00 (q, 1H, J = 6.5 Hz, $H_{3''}$), 3.80 (s, 1H, OH), 2.59 (t, 2H, J = 7.6 Hz, $H_{7''}$), 2.56 (s, 2H, H_2), 2.04 (m, 1H, $H_{3'}$), 1.79 (d, 1H, J = 15.4 Hz, $H_{2'e}$), 1.76 (d, 1H, J = 15.4 Hz, $H_{6'e}$), 1.74 (d, 1H, J = 16.0 Hz, $H_{5'e}$), 1.67 (d, 1H, J = 12.4 Hz, $H_{4'e}$), 1.61 (quint, 2H, J = 7.7 Hz, $H_{6''}$), 1.52 (m, 2H, $H_{4''}$), 1.39 (t, 1H, J = 14.5 Hz, $H_{6'a}$), 1.38 (m, 2H, $H_{5''}$), 1.33 (q, 1H, J = 15.1 Hz, $H_{5'a}$), 1.28 (t, 1H, J = 14.0 Hz, $H_{2'a}$), 1.26 (t, 3H, J = 7.2 Hz, CH_3), 1.02 (qd, 1H, J = 12.3 Hz and J = 3.4 Hz, $H_{4'a}$); IR (film) 3410, 1720, 960; MS (FAB$^+$) m/z 339 (M − 2H_2O + H$^+$). Anal. ($C_{23}H_{34}O_4$) C, H, O.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-undec-1-en-1-yl]-1-cyclohexane Acetate (4a) and Ethyl (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-Hydroxy-undec-1-en-1-yl]-1-cyclohexane Acetate (4b).** Compounds **4a** and **4b** were prepared from **37ab** according to the procedure described for **2a** and **2b**. Preparative HPLC (10 μm Nucleosil, 10 × 250 mm, cyclohexane/diethyl ether: 85/15, 4 mL/min; **4a**: 25 min; and **4b**: 29 min) afforded isomers **4a** and **4b** in 42% and 39.5% yield respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.52 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.42 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.15 (q, J = 7.2 Hz, 2H, CH_2-CH$_3$), 3.99 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.42 (m, 1H, $H_{3'}$), 2.40 (s, 2H, H_2), 1.83−1.16 (m, 23H, CH_3, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{10''}$), 1.05 (m, 2H, $H_{2'}$), 0.85 (m, 3H, $H_{11''}$); IR (film) 3400, 1710, 960; MS (IE, 20 eV) m/z = 318 (M − 2H_2O). Anal. ($C_{21}H_{38}O_4$) C, H, O.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-undec-1-en-1-yl]-1-cyclohexane Acetate (4c) and Ethyl (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-undec-1-en-1-yl]-1-cyclohexane Acetate (4d).** Compounds **4c** and **4d** were prepared from **37cd** according to the procedure described for **2a** and **2b**. Preparative HPLC (10 μm Nucleosil, 10 × 250 mm, cyclohexane/diethyl ether: 80/20, 4 mL/min; **4c**: 22 min; and **4d**: 27 min) afforded isomers **4c** and **4d** in 37% and 42.5% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.53 (ABXY, 1H, J = 15.5 Hz and J = 6.1 Hz, $H_{1''}$), 5.42 (ABXY, J = 15.5 Hz and J = 6.1 Hz, 1H, $H_{2''}$), 4.15 (m, J = 7.2 Hz, 2H, CH_2-CH$_3$), 4.0 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.56 (m, 2H, H_2), 2.02 (m, 1H, $H_{3'}$), 1.8−1.2 (m, 23H, CH_3, $H_{4'}$-$H_{6'}$ and $H_{4''}$-$H_{10''}$), 1.01 (m, 2H, $H_{2'}$), 0.85 (t, 3H, $H_{11''}$); IR (film) 3400, 1720, 960; MS (IE, 20 eV) m/z = 336 (M − H_2O). Anal. ($C_{21}H_{38}O_4$) C, H, O.

(1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (5a) and (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (5b).** Compounds **5a** and **5b** were prepared from **38ab** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 50/50) to afford a first separation of the two isomers **5a** and **5b** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 48/52, 15 mL/min; **5a**: 46 min; and **5b**: 62 min). After HPLC chromatography, compounds **5a** and **5b** (white solid, mp = 52 °C) were isolated in, respectively, 47% and 46% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.23 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.51 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.38 (ABXY, J = 15.5 Hz and J = 6.8 Hz, 1H, $H_{2''}$), 5.14 (s, 1H, OH), 3.97 (q, J = 6.4 Hz, 1H, $H_{3''}$), 2.96 (s, 3H, N-CH_3), 2.92 (s, 3H, N-CH_3), 2.58 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.45 (m, 1H, $H_{3'}$), 2.33 (s, 2H, H_2), 1.87 (d, J = 15.3 Hz, 1H, $H_{2'e}$), 1.79 (d, J = 15.3 Hz, 1H, $H_{6'e}$), 1.76 (q, J = 14.9 Hz, 1H, $H_{5'a}$), 1.71 (d, J = 15.3 Hz, 1H, $H_{4'e}$), 1.61 (quint, J = 7.5 Hz, 2H, $H_{6''}$), 1.53 (d, J = 16.3 Hz, 1H, $H_{5'e}$), 1.49 (m, 2H, $H_{4''}$), 1.38 (m, 2H, $H_{5''}$), 1.09 (td, J = 13.8 Hz and J = 4.0 Hz, 1H, $H_{6'a}$), 0.94 (t, J = 12.6 Hz, 1H, $H_{2'a}$), 0.93 (qd, J = 14.9 Hz and J = 3.2 Hz, 1H, $H_{4'a}$); IR (film) 3430, 1620, 1145, 960; MS (FAB$^+$) m/z = 338 (M − 2H_2O + H^+). Anal. ($C_{23}H_{35}NO_3$) C, H, N, O.

Chiral HPLC separation (5 μm Chiralcel OD, 10.5 × 250 mm, heptane/2-propanol: 80/20, 1.1 mL/min; **5bα**: 46 min 30 s; and **5b*β***: 72 min) from racemic diastereoisomer **5b** afforded enantiomers **5bα** and **5b*β***.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (5cd).** Compound **5cd** was prepared from **38cd** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 40/60) to afford the diastereomeric mixture **5cd** which was further purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, ethyl acetate, 12 mL/min, **5c**: 22 min and **5d**: 25 min) in 92% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.72 (d, J = 5.0 Hz, 1H, OH), 5.51 (ABXY, J = 15.4 Hz and J = 6.1 Hz, 1H, $H_{1''}$), 5.37 (ABXY, J = 6.1 Hz and J = 15.4 Hz, 1H, $H_{2''}$), 4.00 (q, J = 6.1 Hz, 1H, $H_{3''}$), 3.02 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.59 (t, J = 7.2 Hz, 2H, $H_{7''}$), 2.51 (m, 2H, H_2), 1.98 (m, 1H, $H_{3'}$), 1.90 (m, 1H, $H_{2'e}$), 1.85 (m, 1H, $H_{6'e}$), 1.73 (m, 1H, $H_{5'e}$), 1.65 (m, 1H, $H_{4'e}$), 1.61 (quint, J = 7.5 Hz, 2H, $H_{6''}$), 1.51 (m, 2H, $H_{4''}$), 1.38 (m, 1H, $H_{6'a}$), 1.34 (m, 2H, $H_{5''}$), 1.30 (m, 1H, $H_{5'a}$), 1.30 (m, 1H, $H_{2'a}$), 1.06 (m, 1H, $H_{4'a}$); IR (film) 3430, 1620, 1145, 960; MS (FAB$^+$) m/z 356 (M − H_2O + H^+). Anal. ($C_{23}H_{35}NO_3$) C, H, N, O.

(1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*-methyl-*N*-phenyl-acetamide (6ab).** Compound **6ab** was prepared from **39ab** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 55/45) to afford the diastereomeric mixture **6ab** which was further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate (75/25), 16 mL/min; **6a**: 42 min; and **6b**: 47 min) in 94% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44 (m, 2H, H_4), 7.36 (m, 1H, H_6), 7.22 (m, 2H, $H_{10''}$), 7.14 (m, 5H, $H_{9''}$, $H_{11''}$ and H_5), 5.47 (ABXY, 1H, J = 15.6 Hz and J = 6.4 Hz, $H_{1''}$), 5.36 (ABXY, 1H, J = 15.6 Hz and J = 6.9 Hz, $H_{2''}$), 5.14 (s, 1H, OH), 3.97 (q, 1H, J = 6.4 Hz, $H_{3''}$), 3.26 (s, 3H, N-CH_3), 2.58 (t, 2H, J = 7.7 Hz, $H_{7''}$), 2.43 (m, 1H, $H_{3'}$), 2.12 (s, 2H, H_2), 1.75 (d, 1H, J = 14.1 Hz, $H_{2'e}$), 1.75 (q, 1H, J = 15.1 Hz, $H_{5'a}$), 1.70 (d, 1H, J = 15.8 Hz, $H_{6'e}$), 1.68 (d, 1H, J = 16.8 Hz, $H_{4'e}$), 1.61 (quint, 2H, J = 8.4 Hz, $H_{6''}$), 1.50 (m, 2H, $H_{4''}$), 1.50 (d, 1H, J = 15.1 Hz, $H_{5'e}$), 1.36 (m, 2H, $H_{5''}$), 0.91 (td, 1H, J = 16.0 Hz and J = 4.2 Hz, $H_{6'a}$), 0.85 (qd, 1H, J = 14.6 Hz and J = 3.1 Hz, $H_{4'a}$), 0.77 (t, 1H, J = 14.3 Hz, $H_{2'a}$); IR (film) 3400, 1625, 1110, 960. Anal. ($C_{28}H_{37}NO_3$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*-methyl-*N*-phenyl-acetamide (6cd).** Compound **6cd** was prepared from **39cd** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 50/50) to afford the diastereomeric mixture **6cd** which was further purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, ethyl acetate, 5 mL/min; **6c**: 26 min, and **6d**: 28 min) in 93% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44 (m, 2H, H_4), 7.36 (m, 1H, H_6), 7.22 (m, 2H, $H_{10''}$), 7.14 (m, 5H, $H_{9''}$, $H_{11''}$ and H_5), 6.00 (d, 1H, OH), 5.51 (ABXY, J = 15.4 Hz and J = 6.3 Hz, 1H, $H_{1''}$), 5.37 (ABXY, J = 15.4 Hz and J = 6.7 Hz, 1H, $H_{2''}$), 3.99 (q, J = 6.7 Hz, 1H, $H_{3''}$), 3.26 (s, 3H, N-CH_3), 2.59 (t, J = 7.2 Hz, 2H, $H_{7''}$), 2.32 and 2.26 (AB, J = 15.8 Hz, 2H, H_2), 1.90 (m, 1H, $H_{3'}$), 1.87 (m, 1H, $H_{2'e}$), 1.81 (m, 1H, $H_{6'e}$), 1.73 (m, 1H, $H_{5'e}$), 1.66 (m, 1H, $H_{4'e}$), 1.59 (m, 2H, $H_{6''}$), 1.52 (m, 2H, $H_{4''}$), 1.37 (m, 1H, $H_{6'a}$), 1.36 (m, 2H, $H_{5''}$), 1.28 (m, 1H, $H_{2'a}$), 1.22 (m, 1H, $H_{5'a}$), 1.04 (m, 1H, $H_{4'a}$); IR (film) 3400, 1625, 1110, 960. Anal. ($C_{28}H_{37}NO_3$) C, H, N, O.

(1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dipropyl-acetamide (7ab).** Compound **7ab** was prepared from **40ab** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 60/40) to afford the diastereomeric mixture **7ab** which was further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate (75/25), 16 mL/min; **7a**: 35 min; and **7b**: 40 min) in 93% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$, $H_{11''}$), 5.52 (ABXY, J = 15.2 Hz and J = 6.4 Hz, 1H, $H_{1''}$), 5.41 (s, 1H, OH), 5.37 (ABXY, J = 15.2 Hz and J = 6.8 Hz, 1H, $H_{2''}$), 3.99 (q, J = 6.5 Hz, 1H, $H_{3''}$), 3.28 and 3.25 (m, J = 7.7 Hz, 3H, H_6), 3.15 (m, J = 7.7 Hz, 3H, H_3), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.47 (m, 1H, $H_{3'}$), 2.33 (s, 2H, H_2), 1.85 (d, J = 14.2 Hz, 1H, $H_{2'e}$), 1.78 (q, J = 15.2 Hz, 1H, $H_{5'a}$), 1.77 (d, J = 14.2 Hz, 1H, $H_{6'e}$), 1.71 (d, J = 15.5 Hz, 1H, $H_{4'e}$), 1.60 (quint, J = 8.2 Hz, 2H, $H_{6''}$), 1.56 (sext, J = 8.2 Hz, 3H, H_4), 1.55 (sext, J = 8.2 Hz, 3H, H_7), 1.55 (d, J = 15.1 Hz, 1H, $H_{5'e}$), 1.51 (m, 2H, $H_{4''}$), 1.36 (m, 2H, $H_{5''}$), 1.09 (td, J = 13.3 Hz and J = 4.4 Hz, 1H, $H_{6'a}$), 0.94 (t, J = 14.2 Hz, 1H, $H_{2'a}$), 0.94 (qd, J = 15.2 Hz and J = 3.2 Hz, 1H, $H_{4'a}$), 0.90 (t, J = 7.4 Hz, 3H, H_5), 0.87 (t, J = 7.4 Hz, 3H, H_8); IR (film) 3400, 1605, 1140, 960; MS (FAB$^+$) m/z 394 (M − 2H_2O + H^+). Anal. ($C_{27}H_{43}NO_3$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(*E*)-3-hydroxy-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dipropyl-acetamide (7cd).** Compound **7cd** was prepared from **40cd** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 55/45) to afford the diastereomeric mixture **7cd** which was further purified by preparative HPLC (10 μm Rsil, 22 × 250 mm, cyclohexane/ethyl acetate (75/25), 5.4 mL/min; **7c**: 44 min; and **7d**: 55 min) in 91% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$, $H_{11''}$), 6.00 (d, 1H, OH), 5.51 (ABXY, J = 15.4 Hz and J = 6.3 Hz, 1H, $H_{1''}$), 5.37 (ABXY, J = 15.4 Hz and J = 6.7 Hz, 1H, $H_{2''}$), 4.00 (q, J = 6.7 Hz, 1H, $H_{3''}$), 3.31 and 3.22 (m AB, 2H, H_6), 3.19 (m, 2H, H_3), 2.59 (t, J = 7.2 Hz, 2H, $H_{7''}$), 2.54 and 2.47 (AB, J = 15.8 Hz, 2H, H_2), 1.92 (m, 1H, $H_{3'}$), 1.88 (m, 1H, $H_{2'e}$), 1.82 (m, 1H, $H_{6'e}$), 1.75 (m, 1H, $H_{5'e}$), 1.66 (m, 1H, $H_{4'e}$), 1.60 (m, 2H, $H_{6''}$), 1.55 (m, 2H, H_4), 1.52 (m, 2H, H_7), 1.38 (m, 2H, $H_{4''}$), 1.38 (m, 1H, $H_{6'a}$), 1.36 (m, 2H, $H_{5''}$), 1.29 (m, 1H, $H_{2'a}$), 1.23 (m, 1H, $H_{5'a}$), 1.05 (m, 1H, $H_{4'a}$), 0.92 (t, J = 7.6 Hz, 3H, H_5), 0.88 (m, 3H, H_8); IR (film) 3400, 1605, 1140, 960. Anal. ($C_{27}H_{43}NO_3$) C, H, N, O.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(*E*)-3-oxo-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (8ab).** A solution of compound **3a** (120 mg, 0.320 mmol) in dichloromethane (10 mL) and manganese(IV) oxide on activated carbon (840 mg, 4.83 mmol) was stirred for 16 h at room temperature. The reaction mixture was filtrered on Celite and the cake washed with dichloromethane. The filtrate was evaporated and the resulting residue (yellowish oil) purified by column chromatography

on silica gel. Elution with cyclohexane/diethyl ether (75/25) gave the title compound **8ab** as a colorless oil (72 mg, 60%). Several attemps of continuous Soxhlet extraction (acetone, methanol) were made in order to improve the yield but none were successful: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 6.69 (ABX, J = 16.0 Hz and J = 6.9 Hz, 1H, $H_{1''}$), 6.02 (ABX, J = 1.2 Hz and J = 16.0 Hz, 1H, $H_{2''}$), 4.16 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.63 (m, 1H, $H_{3'}$), 2.60 (m, 2H, $H_{4''}$), 2.51 (t, J = 6.9 Hz, 2H, $H_{7''}$), 2.42 (s, 2H, H_2), 1.81 (m, 1H, $H_{2'e}$), 1.78 (m, 2H, $H_{4'e}$ and $H_{5'a}$), 1.75 (m, 1H, $H_{6'e}$), 1.62 (m, 4H, $H_{5''}$ and $H_{6''}$), 1.60 (m, 1H, $H_{5'e}$), 1.26 (t, J = 7.2, 3H, CH_3), 1.20 (m, 1H, $H_{6'a}$), 1.10 (t, J = 12.7 Hz, 1H, $H_{2'a}$), 1.02 (m, 1H, $H_{4'a}$); IR (film) 3410, 1720; MS (IE, 70 eV) m/z 354 (M−H_2O). Anal. ($C_{23}H_{32}O_4$) C, H, O.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(3*R**,*S**)-3-hydroxy-7-phenylheptan-1-yl]-1-cyclohexane Acetate (9b).** To a solution of compound **3b** (72 mg, 0.191 mmol) in ethanol (5 mL) in a 25 mL round-bottom flask was added a 1% aqueous solution of sodium nitrite (100 μL). After being stirred for 30 min, the solution was treated with 10% palladium on activated carbon (19 mg). The flask walls were rinsed with ethanol (2 mL), and the reaction mixture was hydrogenated for 16 h at room temperature. The medium was taken up with 3 mL of diethyl ether which caused the catalyst to precipitate. After filtration over Celite, the cake was rinsed with diethyl ether (3 × 10 mL) and the filtrate concentrated. The filtrate was evaporated, and the resulting residue (80 mg) obtained as a colorless oil was purified by column chromatography on silica gel. Elution with cyclohexane/diethyl ether (65/35) afforded the title compound **9b** (61 mg, 0.162 mmol) as a white solid (mp = 54 °C) in 87% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 4.15 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.52 (m, 1H, $H_{3''}$), 3.30 (s, 1H, OH), 2.60 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.39 (s, 2H, H_2), 1.75 (d, J = 15.9 Hz, 1H, $H_{2'e}$), 1.73 (m, 1H, $H_{3'}$), 1.73 (d, J = 15.9 Hz, 1H, $H_{4'e}$), 1.72 (d, J = 15.9 Hz, 1H, $H_{6'e}$), 1.68 (m, 1H, $H_{5'a}$), 1.62 (m, 2H, $H_{6''}$), 1.53 (d, J = 13.3 Hz, 1H, $H_{5'e}$), 1.42 (m, 2H, $H_{4''}$), 1.41 (m, 2H, $H_{2''}$), 1.39 (m, 2H, $H_{5''}$), 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.28 and 1.15 (m, 2H, $H_{1''}$), 1.18 (td, J = 13.3 Hz and J = 4.3 Hz, 1H, $H_{6'a}$), 0.88 (t, J = 12.4 Hz, 1H, $H_{2'a}$), 0.77 (qd, J = 11.8 Hz and J = 3.6 Hz, 1H, $H_{4'a}$); IR (film) 3410, 1720; MS (FAB$^+$, NBA) m/z 341 (M − 2H_2O + H^+). Anal. ($C_{23}H_{36}O_4$) C, H, O.

Methyl (3*S,*R**,*Z*)-3-[(3*S**,*R**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl]cyclohexylidene Acetate (10a) and Methyl (3*S**,*R**,*Z*)-3-[(3*R**,*S**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1- yl]-cyclohexylidene Acetate (10b).** Compounds **10a** and **10b** were prepared from **41ab** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 85/15) to afford the diastereomeric mixture **10ab** in 94% yield. Further preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 93/7, 15 mL/min; **10a**: 64 min; and **10b**: 71 min) afforded isomers **10a** and **10b** in 45% and 44% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.64 (s, 1H, H_2), 5.60 (ABXY, 1H, J = 15.5 Hz and J = 6.6 Hz, $H_{1''}$), 5.47 (ABXY, 1H, J = 6.8 Hz and J = 15.5 Hz, $H_{2''}$), 4.02 (q, 1H, J = 6.4 Hz, $H_{3''}$), 3.70 (m, 1H, $H_{2'e}$), 3.67 (s, 3H, OMe), 2.60 (t, 2H, J = 7.7 Hz, $H_{7''}$), 2.25 (d, 1H, J = 12.7 Hz, $H_{6'e}$), 2.17 (m, 1H, $H_{3'}$), 2.11 (td, 1H, J = 12.7 Hz and J = 4.6 Hz, $H_{6'a}$), 1.91 (m, 1H, $H_{5'e}$), 1.90 (m, 1H, $H_{2'a}$), 1.82 (m, 1H, $H_{4'e}$), 1.62 (m, 2H, $H_{6''}$), 1.50 (m, 2H, $H_{4''}$), 1.47 (m, 1H, $H_{5'a}$), 1.38 (m, 2H, $H_{5''}$), 1.32 (m, 1H, $H_{4'a}$); IR (film) 3400, 1710, 1640, 960; MS (FAB$^+$) m/z 325 (M − H_2O + H^+). Anal. ($C_{22}H_{30}O_3$) C, H, O.

Chiral HPLC separation (5 μm Chiralcel OD, 10.5 × 250 mm, heptane/2-propanol: 90/10, 1.7 mL/min; **10bα**: 32 min; and **10b*β***: 50 min) from the racemic diastereoisomer **10b** afforded enantiomers **10bα** and **10b*β***.

Methyl (*E*)-3-[(*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl]-cyclohexylidene Acetate (10cd). Compound **10cd** was prepared from **41cd** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 85/15) to afford the diastereomeric mixture **10cd** in 96% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.61 (s, 1H, H_2), 5.54 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.42 (ABXY, J = 6.5 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 4.01 (q, J = 6.4 Hz, 1H, $H_{3''}$), 3.66 (s, 3H, OMe), 3.65 (d, J = 13.7 Hz, 1H, $H_{6'e}$), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.26 (m, 1H, $H_{2'e}$), 2.15 (m, 1H, $H_{3'}$), 1.99 (m, 1H, $H_{6'a}$), 1.97 (m, 1H, $H_{2'a}$), 1.89 (m, 1H, $H_{5'e}$), 1.79 (m, 1H, $H_{4'e}$), 1.60 (quint, J = 7.5 Hz, 2H, $H_{6''}$), 1.49 (m, 2H, $H_{4''}$), 1.42 (m, 1H, $H_{5'a}$), 1.35 (m, 2H, $H_{5''}$), 1.29 (m, 1H, $H_{4'a}$); IR (film) 3400, 1710, 1640, 960; MS (FAB$^+$) m/z 309 (M − H_2O − Me). Anal. ($C_{22}H_{30}O_3$) C, H, O.

[(3*S,*R**,*Z*)-3-((3*S**,*R**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (11a) and [(3*S**,*R**,*Z*)-3-((3*R**,*S**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (11b).** Compounds **11a** and **11b** were prepared from **42ab** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 50/50) to afford the diastereomeric mixture **11ab** in 92% yield. Further preparative HPLC (5 μm Inertsil, 20 × 250 mm, diethyl ether/ethyl acetate: 85/15, 15 mL/min; **11a**: 41 min 30 s; and **11b**: 50 min 30 s) afforded isomers **11a** and **11b** in 45% and 44% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.72 (s, 1H, H_2), 5.57 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.42 (ABXY, J = 6.8 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 3.98 (q, J = 6.5 Hz, 1H, $H_{3''}$), 2.98 (s, 3H, N-CH_3), 2.93 (s, 3H, N-CH_3), 2.89 (d, J = 13.2 Hz, 1H, $H_{2'e}$), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.21 (d, J = 13.9 Hz, 1H, $H_{6'e}$), 2.14 (m, 1H, $H_{3'}$), 2.05 (td, J = 13.9 Hz and J = 4.7 Hz, 1H, $H_{6'a}$), 1.84 (d, J = 13.9 Hz, 1H, $H_{5'e}$), 1.79 (t, J = 13.2 Hz, 1H, $H_{2'a}$), 1.74 (d, J = 8.5 Hz, 1H, $H_{4'e}$), 1.61 (quint, J = 8.0 Hz, 2H, $H_{6''}$), 1.49 (m, 2H, $H_{4''}$), 1.43 (m, J = 13.9 Hz, 1H, $H_{5'a}$), 1.35 (m, 2H, $H_{5''}$), 1.26 (mt, J = 13.9 Hz, 1H, $H_{4'a}$); IR (film) 3400, 1640, 1630, 1135, 960; MS (FAB$^+$) m/z 338 (M − H_2O + H^+). Anal. ($C_{23}H_{33}NO_2$) C, H, N, O.

[(3*S,*R**,*E*)-3-((3*S**,*R**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (11c) and [(3*S**,*R**,*E*)-3-((3*R**,*S**,*E*)-3-Hydroxy-7-phenyl-1-hepten-1-yl)cyclohexylidene]-*N*,*N*-dimethyl-acetamide (11d).** Compounds **11c** and **11d** were prepared from **42cd** according to the procedure described for **2a** and **2b**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/ethyl acetate, 50/50) to afford the diastereomeric mixture **11cd** in 95% yield. Further preparative HPLC (5 μm Inertsil, 20 × 250 mm, diethyl ether/ethyl acetate: 85/15, 15 mL/min; **11c**: 43 min; and **11d**: 52 min) afforded isomers **11c** and **11d** in 46% and 45% yield, respectively: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.71 (s, 1H, H_2), 5.56 (ABXY, J = 15.5 Hz and J = 6.5 Hz, 1H, $H_{1''}$), 5.42 (ABXY, J = 6.5 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 4.02 (q, J = 6.5 Hz, 1H, $H_{3''}$), 3.00 (s, 3H, N-CH_3), 2.95 (s, 3H, N-CH_3), 2.86 (d, J = 12.6 Hz, 1H, $H_{6'e}$), 2.60 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.24 (d, J = 12.1 Hz, 1H, $H_{2'e}$), 2.14 (m, 1H, $H_{3'}$), 1.93 (t, J = 12.1 Hz, 1H, $H_{2'a}$), 1.86 (t, J = 12.6 Hz, 1H, $H_{6'a}$), 1.83 (m, 1H, $H_{5'e}$), 1.78 (m, 1H, $H_{4'e}$), 1.63 (quint, J = 7.6 Hz, 2H, $H_{6''}$), 1.49 (m, 2H, $H_{4''}$), 1.38 (q, J = 12.6 Hz, 1H, $H_{5'a}$), 1.33 (m, 2H, $H_{5''}$), 1.23 (qd, J = 12.6 Hz and J = 2.9 Hz, 1H, $H_{4'a}$); IR (film) 3400, 1675, 1600, 960; MS (FAB$^+$) m/z 338 (M − H_2O + H^+). Anal. ($C_{23}H_{33}NO_2$) C, H, N, O.

[(3*S,*R**,*Z*)-3-((3*S**,*R**,*E*)-3-[(*E*)-3-Acetoxy-7-phenyl-1-hepten-1-yl]cyclohexylidene-*N*,*N*-dimethyl-acetamide (12a) and [(3*S**,*R**,*Z*)-3-((3*R**,*S**,*E*)-3-[(*E*)-3-Acetoxy-7-phenyl-1-hepten-1-yl]cyclohexylidene-*N*,*N*-dimethyl-acetamide (12b).** To compound **42ab** (100 mg, 0.213 mmol) stirred in a 5 mL round-bottom flask were added under nitrogen at 0 °C acetic anhydride (0.9 mL, 9.5 mmol) and dry ferric chloride (35 mg, 0.213 mmol). The flask walls were rinsed with acetic anhydride (0.3 mL, 3.2 mmol), and the reaction mixture was stirred for 15 min at 0 °C. The medium was hydrolyzed with saturated $NaHCO_3$ (3 mL), ethyl acetate (10 mL) was added, and stirring was continued for 10 min. The water layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (3 mL)

and with brine (3 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue (110 mg) obtained as an orange oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 60/40) to afford a mixture of isomers **12ab** and **43ab** in the ratio 81:19. Further preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 90/10, 15 mL/min; **12a**: 35 min; **12b**: 41 min; **43a**: 50 min; and **43b**: 62 min) afforded the isolation of isomers in 81% for **12** and 18% for **43**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H, $H_{10''}$), 7.19 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.78 (s, 1H, H_2), 5.66 (ABXY, J = 15.5 Hz and J = 6.3 Hz, 1H, $H_{1''}$), 5.39 (ABXY, J = 7.2 Hz and J = 15.5 Hz, 1H, $H_{2''}$), 5.19 (q, J = 6.7 Hz, 1H, $H_{3''}$), 3.03 (s, 3H, N-CH_3), 3.02 (m, 1H, $H_{2'e}$), 2.99 (s, 3H, N-CH_3), 2.61 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.26 (d, J = 13.1 Hz, 1H, $H_{6'e}$), 2.04 (s, 3H, CH_3CO), 2.2−1.2 (m, 13H, $H_{2'a}$, $H_{3''}$-$H_{5'}$, $H_{6'a}$, $H_{4''}$-$H_{6''}$); IR (film) 1640, 1630, 1135, 960. Anal. ($C_{25}H_{35}NO_3$) C, H, N, O.

(*Z*)-3-[(*E*)-1-Acetoxy-7-phenylhept-2-en-1-yl]cyclohexylidene-*N*,*N*-dimethyl-acetamide (43ab): ^{1}H NMR (360 MHz, $CDCl_3$) 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.73 (s, 1H, H_2), 5.67 (ABXY$_2$, J = 15.4 Hz and J = 7.1 Hz, 1H, $H_{3''}$), 5.33 (ABXY$_2$, J = 8.0 Hz and J = 15.4 Hz, 1H, $H_{2''}$), 5.04 (t, J = 7.2 Hz, 1H, $H_{1''}$), 2.98 (s, 3H, N-CH_3), 2.93 (s, 3H, N-CH_3), 2.85 (d, J = 12.8 Hz, 1H, $H_{2'e}$), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.22 (d, J = 13.3 Hz, 1H, $H_{6'e}$), 2.04 (q, J = 7.0 Hz, 2H, $H_{4''}$), 2.03 (td, J = 15.0 Hz and J = 4.7 Hz, 1H, $H_{6'a}$), 2.01 (s, 3H, CH_3CO), 1.88 (d, J = 16.8 Hz, 1H, $H_{5'e}$), 1.79 (t, J = 14.1 Hz, 1H, $H_{2'a}$), 1.74 (d, J = 15.0 Hz, 1H, $H_{4'e}$), 1.70 (m, 1H, $H_{3'}$), 1.60 (quint, J = 7.8 Hz, 2H, $H_{6''}$), 1.40 (quint, J = 7.5 Hz, 2H, $H_{5''}$), 1.38 (qt, J = 11.3 Hz and J = 3.2 Hz, 1H, $H_{5'a}$), 1.19 (qd, J = 10.7 Hz and J = 3.2 Hz, 1H, $H_{4'a}$); IR (film) 1640, 1630, 1135, 960; MS (FAB$^+$) m/z 338 (M − OAc). Anal. ($C_{25}H_{35}NO_3$) C, H, N, O.

Methyl 3-(3-Hydroxy-7-phenylheptan-1-yl)cyclohexane-1-Acetate (13). Compound **13** was prepared from **10cd** according to the procedure described for **9b** using twice the proportion of palladium catalyst and sodium nitrite. The residue obtained as a colorless oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 80/20) to afford a first separation of the two isomers **13ab** and **13cd** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 94/6, 18 mL/min; **13cd**: 62 and 63 min 30 s; and **13ab**: 67.5 and 70 min). After HPLC chromatography, compounds **13cd** and **13ab** were isolated in, respectively, 59% and 23% yield.

Methyl (1*R,3*S**)-3-(3-Hydroxy-7-phenylheptan-1-yl)-cyclohexane-1-Acetate (13ab):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 3.64 (s, 3H, OCH_3), 3.52 (m, 1H, $H_{3''}$), 2.60 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.17 (d, J = 6.8 Hz, 2H, H_2), 1.76 (m, 1H, $H_{1'}$), 1.72 (d, J = 15.1 Hz, 1H, $H_{2'e}$), 1.72 (d, J = 17.4 Hz, 1H, $H_{5'e}$), 1.71 (d, J = 15.1 Hz, 1H, $H_{6'e}$), 1.70 (d, J = 16.3 Hz, 1H, $H_{4'e}$), 1.62 (m, 2H, $H_{6''}$), 1.43 (m, 2H, $H_{4''}$), 1.42 (m, 2H, $H_{2''}$), 1.41 (m, 2H, $H_{5''}$), 1.26 (q, J = 15.7 Hz, 1H, $H_{5'a}$), 1.25 (m, 1H, $H_{3'}$), 1.17 and 1.31 (m, 2H, $H_{1''}$), 1.18 (qd, J = 11.9 Hz and J = 3.6 Hz, 1H, $H_{6'a}$), 0.77 (q, J = 16.2 Hz, 1H, $H_{4'a}$), 0.61 (q, J = 11.6 Hz, 1H, $H_{2'a}$); IR (film) 3410, 1720; MS (FAB$^+$) m/z 329 (M − H_2O + H$^+$). Anal. ($C_{22}H_{34}O_3$) C, H, O.

Methyl (1*S,3*S**)-3-(3-Hydroxy-7-phenylheptan-1-yl)-cyclohexane-1-Acetate (13cd):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.16 (m, 3H, $H_{9''}$ and $H_{11''}$), 3.64 (s, 3H, OCH_3), 3.55 (m, 1H, $H_{3''}$), 2.61 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.25 (d, J = 7.3 Hz, 2H, H_2), 2.13 (m, 1H, $H_{1'}$), 1.7−1.1 (m, 19H, $H_{2'}$-$H_{6'}$, $H_{1''}$-$H_{2''}$ and $H_{4''}$-$H_{6''}$); IR (film) 3410, 1720; MS (FAB$^+$) m/z 329 (M − H_2O + H$^+$). Anal. ($C_{22}H_{34}O_3$) C, H, O.

Ethyl 1-Hydroxy-3-[(*E*)-3-ethyl Acetate-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (14). Compound **14** was prepared from **44** according to the procedure described for **25** using 2.5 equiv of lithiated ethyl acetate. The residue obtained as a colorless oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 80/20) to afford a first separation of the four isomers **14a**, **14b**, **14c**, and **14d** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 90/10, 15 mL/min; **14a**: 51 min; and **14b**: 54 min; cyclohexane/ethyl acetate: 85/15, 15 mL/min; **14c**: 36 min; and **14d**: 43 min). After HPLC chromatography, compounds **14a**, **14b**, **14c**, and **14d** were isolated in, respectively, 32%, 2.6%, 26%, and 23% yield.

Ethyl (1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-ethyl Acetate-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (14a) and Ethyl (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-ethyl Acetate-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (14b):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.53 (ABX, J = 15.8 Hz and J = 6.8 Hz, 1H, $H_{1''}$), 5.35 (ABX, J = 16.0 Hz, 1H, $H_{2''}$), 4.15 (q, J = 7.2 Hz, 2H, CH_2), 4.10 (q, J = 7.2 Hz, 2H, CH_2), 3.81 (s, 1H, OH), 3.38 (s, 1H, OH cycle), 2.58 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.47 (s, 2H, H_4), 2.42 (m, 1H, $H_{3'}$), 2.40 (s, 2H, H_2), 1.73 (d, J = 15.4 Hz, 1H, $H_{2'e}$), 1.72 (d, J = 15.4 Hz, 1H, $H_{6'e}$), 1.72 (d, J = 15.4 Hz, 1H, $H_{5'a}$), 1.66 (d, J = 15.4 Hz, 1H, $H_{4'e}$), 1.58 (m, 2H, $H_{6''}$), 1.55 (d, J = 13.0 Hz, 1H, $H_{5'e}$), 1.50 (m, 2H, $H_{4''}$), 1.36 (m, 2H, $H_{5''}$), 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 1.18 (td, J = 13.7 Hz and J = 4.0 Hz, 1H, $H_{6'a}$), 1.02 (t, J = 12.9 Hz, 1H, $H_{2'a}$), 0.92 (qd, J = 12.8 Hz and J = 3.4 Hz, 1H, $H_{4'a}$); IR (film) 3410, 1720, 960; MS (FAB$^+$) m/z 425 (M − 2H_2O + H$^+$). Anal. ($C_{27}H_{40}O_6$) C, H, O.

Ethyl (1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-ethyl Acetate-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (14c) and Ethyl (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-ethyl Acetate-3-hydroxy-7-phenyl-1-hepten-1-yl]-1-cyclohexane Acetate (14d):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.56 (ABX, J = 15.6 Hz and J = 6.6 Hz, 1H, $H_{1''}$), 5.35 (ABX, J = 16.2 Hz, 1H, $H_{2''}$), 4.16 (q, J = 7.0 Hz, 2H, CH_2), 4.11 (q, J = 6.9 Hz, 2H, CH_2), 3.80 (s, 1H, OH), 3.75 (s, 1H, OH cycle), 2.57 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.56 (s, 2H, H_2), 2.47 (s, 2H, H_4), 2.03 (m, 1H, $H_{3'}$), 1.75 (d, J = 15.8 Hz, 1H, $H_{6'e}$), 1.71 (d, J = 18.4 Hz, 1H, $H_{5'e}$), 1.71 (d, J = 15.8 Hz, 1H, $H_{2'e}$), 1.64 (d, J = 15.8 Hz, 1H, $H_{4'e}$), 1.57 (m, 2H, $H_{6''}$), 1.46 (m, 2H, $H_{4''}$), 1.39 (t, J = 15.1 Hz, 1H, $H_{6'a}$), 1.34 (m, 2H, $H_{5''}$), 1.29 (m, 1H, $H_{5'a}$), 1.26 (t, J = 13.8 Hz, 1H, $H_{2'a}$), 1.26 (t, J = 7.0 Hz, 3H, CH_3), 1.23 (t, J = 7.0 Hz, 3H, CH_3), 0.98 (qd, J = 12.2 Hz and J = 3.6 Hz, 1H, $H_{4'a}$); IR (film) 3410, 1720, 960; MS (FAB$^+$) m/z 443 (M − H_2O + H$^+$). Anal. ($C_{27}H_{40}O_6$) C, H, O.

1-Hydroxy-3-[(*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (15). Compound **15** was prepared by condensation of *N*,*N*-dimethylacetamide on **46** according to the procedure described for **25**. The residue obtained as an oil was purified by column chromatography on silica gel (eluent: cyclohexane/diethyl ether, 60/40) to afford a first separation of the four isomers **15a**, **15b**, **15c**, and **15d** which were further purified by preparative HPLC (5 μm Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 40/60, 15 mL/min, **15a**: 24 min; **15b**: 26 min; **15c**: 38 min 30 s; and **15d**: 42 min 30 s). After HPLC chromatography, compounds **15a**, **15b**, **15c**, and **15d** were isolated in, respectively, 25%, 26%, 15%, and 16% yield.

(1*S,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (15a) and (1*S**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (15b):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.23 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.47 (ABX, 1H, J = 4.0 Hz, $H_{1''}$), 5.46 (AB, 1H, $H_{2''}$), 5.13 (s, 1H, OH cycle), 2.98 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.58 (t, 2H, J = 7.7 Hz, $H_{7''}$), 2.46 (m, 1H, $H_{3'}$), 2.35 (s, 2H, H_2), 1.86 (d, 1H, J = 14.2 Hz, $H_{2'e}$), 1.81 (d, 1H, J = 14.2 Hz, $H_{6'e}$), 1.79 (q, 1H, J = 13.4 Hz, $H_{5'a}$), 1.71 (d, 1H, J = 13.4 Hz, $H_{4'e}$), 1.56 (quint, 2H, J = 7.7 Hz, $H_{6''}$), 1.54 (d, 1H, J = 14.2 Hz, $H_{5'e}$), 1.51 (m, 2H, $H_{4''}$), 1.38 (quint, 2H, J = 7.7 Hz, $H_{5''}$), 1.21 (s, 3H, CH_3), 1.09 (td, 1H, J = 13.8 Hz and J = 4.0 Hz, $H_{6'a}$), 0.95 (t, 1H, J = 12.6 Hz, $H_{2'a}$), 0.93 (qd, 1H, J = 13.2 Hz and J = 4.0 Hz, $H_{4'a}$); IR (film) 3430, 1620, 1145, 970; MS (FAB$^+$) m/z 370 (M − H_2O+H$^+$). Anal. ($C_{24}H_{37}NO_3$) C, H, N, O.

Chiral HPLC separation (5 μm Chiralcel OD, 10.5 × 250 mm, heptane/2-propanol: 80/20, 1.125 mL/min; **15bα**: 42 min;

and **15bβ**: 47 min) from racemic diastereoisomer **15b** afforded enantiomers **15bα** and **15bβ**.

(1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (15c) and (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-hydroxy-3-methyl-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (15d):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (m, 2H, $H_{10''}$), 7.14 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.69 (s, 1H, OH), 5.51 (ABX, J = 15.8 Hz and J = 5.8 Hz, 1H, $H_{1''}$), 5.44 (AB, J = 15.8 Hz, 1H, $H_{2''}$), 3.01 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.58 (t, J = 7.6 Hz, 2H, $H_{7''}$), 2.53 and 2.48 (AB, J = 16.2 Hz, 2H, H_2), 1.97 (m, 1H, $H_{3'}$), 1.87 (m, 1H, $H_{2'a}$), 1.83 (m, 1H, $H_{6'a}$), 1.73 (m, 1H, $H_{5'a}$), 1.67 (m, 1H, $H_{4'e}$), 1.58 (m, 2H, $H_{6''}$), 1.50 (m, 2H, $H_{4''}$), 1.40 (m, 1H, $H_{6'e}$), 1.32 (m, 2H, $H_{5''}$), 1.28 (m, 1H, $H_{2'e}$), 1.24 (m, 1H, $H_{5'e}$), 1.21 (s, 3H, CH_3), 1.01 (qd, J = 11.9 Hz and J = 3.6 Hz, 1H, $H_{4'a}$); IR (film) 3430, 1620, 1145, 970; MS (FAB$^+$) m/z 370 (M − H_2O + H^+). Anal. ($C_{24}H_{37}NO_3$) C, H, N, O.

1-Hydroxy-3-[(*E*)-3-fluoro-7-phenyl-1-hepten-1-yl]cyclohexane-1-*N*,*N*-dimethyl-acetamide (16). Compound **16** was prepared by condensation of *N*,*N*-dimethylacetamide on **49** according to the procedure described for **25**. The residue obtained as an oil was purified by column chromatography on silica gel. Elution of diethyl ether afforded a first separation of the two isomers **16ab** and **16cd** which were further purified by preparative HPLC (5 μM Inertsil, 20 × 250 mm, cyclohexane/ethyl acetate: 75/25, 15 mL/min; **16a**: 44 min; **16b**: 48 min; **16c**: 58 min; and **16d**: 60 min). After HPLC chromatography, compounds **16a**, **16b, 16c,** and **16d** were isolated in, respectively, 30, 28, 14, and 12% yield.

(1*S,3*R**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-fluoro-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (16a) and (1*S**,3*R**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-fluoro-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (16b):** ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (m, 2H, $H_{10''}$), 7.15 (m, 3H, $H_{9''}$ and $H_{11''}$), 5.62 (m, 1H, $H_{1''}$), 5.45 (m, 1H, $H_{2''}$), 5.18 (s, 1H, OH), 4.75 (qd, J = 49.0 Hz and J = 5.6 Hz, 1H, $H_{3''}$), 2.97 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.50 (m, 1H, $H_{3'}$), 2.35 (s, 2H, H_2), 1.89 (d, J = 13.8 Hz, 1H, $H_{2'e}$), 1.80 (d, J = 13.8 Hz, 1H, $H_{6'e}$), 1.79 (q, J = 16.2 Hz, 1H, $H_{5'a}$), 1.74 (d, J = 13.8 Hz, 1H, $H_{4'e}$), 1.64 (m, 2H, $H_{4''}$), 1.62 (m, 2H, $H_{6''}$), 1.54 (d, J = 16.2 Hz, 1H, $H_{5'e}$), 1.39 (m, 2H, $H_{5''}$), 1.09 (td, J = 13.7 Hz and J = 4.2 Hz, 1H, $H_{6'a}$), 0.96 (t, J = 12.5 Hz, 1H, $H_{2'a}$), 0.95 (q, J = 15.4 Hz, 1H, $H_{4'a}$); ^{19}F NMR (235 MHz, $CDCl_3$) δ −169.8 (m); IR (film) 3430, 1620, 1145, 960; MS (FAB$^+$) m/z 356 (M − HF + H^+). Anal. ($C_{23}H_{34}NO_2F$) C, H, N, O.

(1*R,3*S**)-1-Hydroxy-3-[(3*S***R**,*E*)-3-fluoro-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (16c) and (1*R**,3*S**)-1-Hydroxy-3-[(3*R***S**,*E*)-3-fluoro-7-phenyl-1-hepten-1-yl]cyclohexane-*N*,*N*-dimethyl-acetamide (16d):** ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5H, $H_{9''}$-$H_{11''}$), 5.73 (s, 1H, OH), 5.57 (m, 2H, $H_{2''}$ and $H_{1''}$), 4.75 (qd, J = 49.0 Hz and J = 5.6 Hz, 1H, $H_{3''}$), 3.01 (s, 3H, N-CH_3), 2.95 (s, 3H, N-CH_3), 2.59 (t, J = 7.7 Hz, 2H, $H_{7''}$), 2.51 (m, 2H, H_2), 0.8−2.2 (m, 15H, $H_{2'}$-$H_{6'}$ and $H_{4''}$-$H_{6''}$); ^{19}F NMR (235 MHz, $CDCl_3$) δ −170.4 (md, J = 48.9 Hz), −170.5 (md, J = 49.2 Hz); IR (film) 3430, 1620, 1145, 960. Anal. ($C_{23}H_{34}NO_2F$) C, H, N, O.

General Procedure for the Preparation of Sodium salts. To a 0.01 M solution of the pure ester in 1:1 MeOH/H_2O at 0 °C was added 1.5 equiv of 0.1 N NaOH, and the solution was stirred at 25 °C for 16 h. TLC analysis indicated all the starting ester was consumed.

Biological Evaluation. Human Neutrophil Preparation. Human PMNs were isolated from heparinized venous blood of heatlthy donors by dextran T500 sedimentation as previously described.[35] Supernatant was centrifuged on Ficoll Paque, and residual erythrocytes were removed by hypotonic lysis. PMNs were washed in Hank's balanced salt solution (HBSS) without Ca^{2+} and Mg^{2+}, and cell viability was assessed by trypan blue exclusion.

Guinea Pig Lung Membrane Preparation. Adult male Dunkin Hartley guinea pigs (350−500 g) were used, and all lung membrane preparation was performed at 4 °C as previously described.[36] Briefly, lungs were removed and washed in phosphate buffer saline (PBS) without Ca^{2+} and Mg^{2+}. Lungs were minced and homogenized in 10 mM tris (HCl) buffer, pH 7.4, containing 250 mM sucrose, 100 μM phenylmethylsulfonyl fluoride, and 2 mM dithioerythritol. The homogenate was filtered through two layers of cheesecloth and centrifuged at 1000*g* for 10 min. The supernatant was centrifuged at 45000*g* for 30 min, and the pellet was washed three times in 50 mM tris (HCl) buffer, pH 7.4, containing 20 mM $CaCl_2$. The pellet was then resuspended in the same buffer and stored under liquid nitrogen. The protein concentration was determined by Lowry's method.

LTB_4 Receptor Binding. Binding to PMNs was performed in HBSS without Ca^{2+} and Mg^{2+} containing 5 mM HEPES buffer. PMNs (10^6 cells) were incubated for 20 min at 4 °C with 1 nM [^{3}H] LTB_4 (7.4 TBq/mmol) in the presence or absence of competitors at various concentrations. Binding to guinea pig lung membranes was performed in 50 mM tris (HCl) buffer, pH 7.4, containing 20 mM $CaCl_2$. Membranes (1 mg proteins/mL) were incubated for 30 min at 25 °C with 1 nM [^{3}H] LTB_4 in the presence or absence of competitors. Binding was determined by filtration technique as previously described.[37]

LTB_4-Induced Chemotaxis. PMNs prepared as described above were used. The cells suspended in HBSS without Ca^{2+} and Mg^{2+} were labeled with ^{51}Cr (1 μCi/10^6 cells) for 1 h at 37 °C and washed twice in HBSS. PMNs were finally resuspended at 10^7 cells/mL in Hank's buffer supplemented with 1% bovine serum albumin. LTB_4 and competitors in Hank's buffer were added to the bottom half of Boyden−Keller chambers, two 3 μm cellulose nitrate filters were placed over each well, and the top part of the chambers was filled with cell suspension as previously described.[38] The chambers were incubated at 37 °C in 5% CO_2/95% humidified air for 150 min. Radioactivity on the lower filter was measured by liquid scintillation spectrometry (Beckman LS 3801 counter). Results are expressed as percent of control.

Guinea Pig Lung Parenchymal Strip Contraction. Strips of Dunkin Hartley guinea pig lung parenchyma were cut and placed in 10 mL organ baths containing oxygenated (95% O_2/5% CO_2) Tyrode solution at 37 °C. Strips were recorded on a polygraph with an isometric tension of 400 mg. After a 1 h equilibration, mepyramine (1 μM) and atropine (10 μM) were added to the Tyrode solution and competitors were tested for their agonist activity. Contraction responses were recorded for 5 min. The antagonist activities were tested by adding the drugs to the bath 2 min before LTB_4 (30 nM) stimulation. The results are expressed as percent inhibition of LTB_4-induced contraction.

PMA-Induced Mouse Ear Inflammation Model.[39] Twenty microliters of Phorbol 12-myristate 13-acetate (5 mg in 20 mL ethanol/water: 8/2) was applied topically to the anterior and posterior surfaces of mice right ears, 30 min following similar application of test substance or vehicle (2 × 20 μL at 5 min intervals in absolute ethanol). Mice left ears were used as control. Ear swelling was then measured by a Dyer model micrometer gauge after 6 h as an index of inflammation. Five mice (Iffa Credo, France male 25 ± 2 g) per dose level of test substance were used. For all test procedures, percent inhibition was calculated according to the equation: % = [Ic − It/Ic] × 100 where Ic and It represent the increase in ear thickness (mm) in control and treated mice, respectively. Dexamethasone was used as the positive reference agent in the control group.

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