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Development of Analogues of 1α,25-Dihydroxyvitamin D_3 with Biased Side-Chain Orientation: C20 Methylated Des-C,D-homo Analogues

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Dedicated to Professor Alain Krief

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The discovery that 1α,25-dihydroxyvitamin D_3 is effective in the inhibition of cellular proliferation and in the induction of cellular differentiation has led to a search for analogues in which these activities and the classical calcemic activity of the hormone are dissociated. In this context, the synthesis and biological evaluation are reported for six CD-ring modified structural analogues that were conceived so as to enforce a particular orientation of the 25-hydroxylated side chain. The analogues are characterized by the absence of the C-ring and the presence of an unnatural six-membered D-ring. The biased side-chain orientations are realized through the stereocontrolled incorporation of methyl substituents at positions C13/C20 and C16/C20. Comparison of the results of the biological evaluation and conformational analysis of the side chain confirms the existence of a relationship between inhibition of MCF-7 breast cancer cell proliferation and side chain geometry.

Introduction

1α,25-Dihydroxyvitamin D_3 (**1**, also known as calcitriol) is the hormonally active form of vitamin D (Figure 1).[1] Its potential in therapy is linked to its immunomodulatory activity and to its ability to inhibit cellular proliferation and to induce cellular differentiation. However, as a result of its classical calciotropic activity, its therapeutic value in the treatment of certain cancers is limited, as effective doses generate calcemic side effects.[2] This has instigated an active search for analogues of calcitriol in which the calcemic and antiproliferative or prodifferentiating activities are separated. In this context, various successful structural modifications have been introduced in the side chain or in the A-ring, which are the flexible parts of the molecule.[3] As one example, the inversion of the configuration at C20 in calcitriol leads to derivative **2**, which is several orders of magnitude more potent than natural hormone **1** (Table 1).[4]

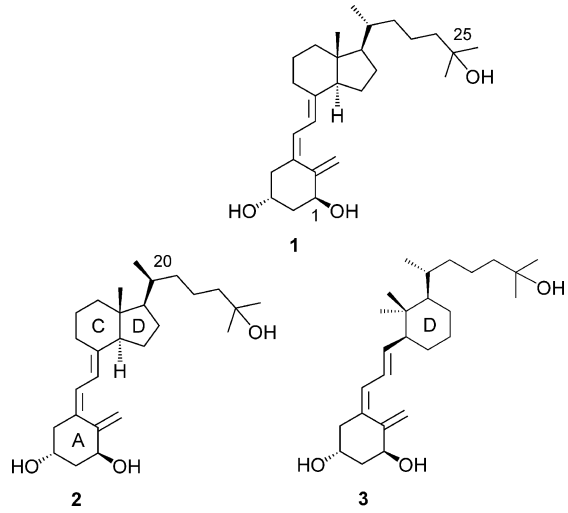

Figure 1. Chemical structures of calcitriol (**1**), 20-*epi*-calcitriol (**2**), and a 6D analogue (**3**).

Our laboratory, in contrast, has focused on modifications in the central CD-ring system.[5] Almost as a rule, these modifications have led to a reduction in calcemic activity.[6] As a typical example, analogue **3**, a "6D analogue" in which the C-ring has been removed (deletion of C9 and C11) and the D-ring enlarged, possesses a similar prodifferentiating activity as the natural hormone, but is much less calcemic (Table 1).[7]

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Table 1. Selected biological activities of **1**–**4**.[a]

Entry	Binding	Cell differentiation and proliferation		Calcium
	VDR (pig)	HL-60	MCF-7	Ca serum (mice)
1	100	100	100	100
2	88	3000	5000	800
3	125	90	300	4
4a	20	90	200	4
4b	2	9	30	<0.25
4c	2	8	70	<0.25

[a] The activities are presented as relative values; the reference value of calcitriol (**1**) is defined as 100%. Further details about the methodology are given in the Experimental Section.

In the present work we will focus on the development of analogues possessing side chains with biased spatial orientations. Studies have shown indeed that for many analogues there is a (qualitative) correlation between cell-differentiating potency and the preferred spatial orientation of the side chain. In particular, it was observed that the preferred side chain orientations of many potent analogues are distributed among a restricted "active" region in space (vide infra).[8]

In particular, we wish to describe the synthesis of 6D analogues, which are conceived so as to favor, among three possible side chain orientations, the one that can be associated with the active region. As shown in Figure 2, the conceived 6D analogues are characterized by a *cis* relation between the alkyl chain at C17 and the seco-B,A-ring part of the molecule at C14. Biased side chain orientations are induced by the incorporation of two methyl groups, each one located at a different position of the three considered positions C13, C16, and C20. Depending on the location of the two methyl groups and the relative configuration of the corresponding stereocenters, one of three possible orientations for the side chain will result. The side chain orientations are identified as S(g+), S(a), and S(g–) depending on the sign and magnitude of the dihedral angle C13–C17–C20–C22 (+60, 180, and –60°, respectively), with C22 representing the first carbon atom of what we will further consider as the side chain S. The S(g+) orientation is the one which directs the 25-hydroxy group towards the desired active region. Among the three possible staggered conformations that result from rotation at the C17–C20 bond, the preferred one will be characterized by minimal steric interactions and in particular by the absence of *syn*-pentane interactions.[9]

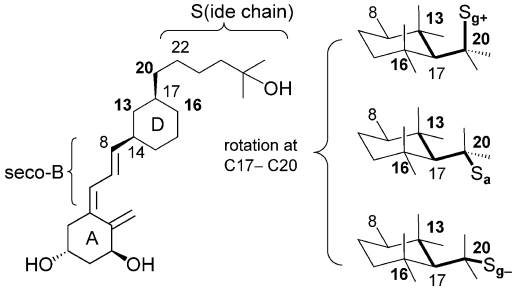


Figure 2. Staggered side-chain orientations in 6D analogues resulting from rotation at the C17–C20 bond.

In this context, we have described in a previous study the three stereoisomeric 6D analogues **4a**, **4b**, and **4c**, featuring the C13/C16 disubstitution pattern (Figure 3).[10] Among the three stereoisomers, **4a** with the side chain in the desired S(g+) orientation was found to be significantly more active than the two other stereoisomers (Table 1).

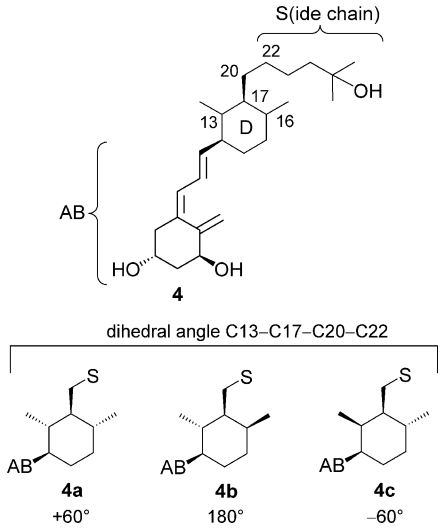


Figure 3. Chemical structures of analogues **4a**, **4b**, and **4c** with dihedral angle value (τ) in the preferred conformation of fragment C13–C17–C20–C22.

Results and Discussion

In the present work we will concentrate on the methyl disubstitution at C13/C20 and at C16/C20. In particular, we describe herein the synthesis and biological evaluation of analogues **5a**, **5b**, **6a**, **6b**, **7a**, and **7b** (Figure 4). These repre-

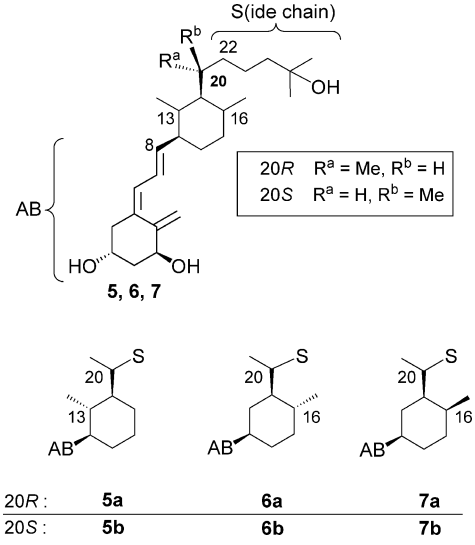


Figure 4. Chemical structures of analogues **5a**, **5b**, **6a**, **6b**, **7a**, and **7b**.

sent three different pairs, each pair including the C20 epimers that are identified as either the **a** (20*R*) or **b** (20*S*) epimer. The three different series **5**, **6**, and **7**, which are differentiated by the location of the second methyl group and by the configuration of the resulting stereocenters at C13 or C16, were chosen so that among the six analogues, two of them would favor each one of the three possible orientations S(g+), S(a), or S(g–). As illustrated in Figure 5, the desired orientation S(g+) is imposed in analogues **5a** and **6b**, the orientation S(a) in analogues **5b** and **7a**, and the orientation S(g–) in analogues **6a** and **7b**. We will not consider here two further analogues that would correspond to the 13-*epi*-**5** series featuring three vicinal substituents in the all-*cis* configuration, and in which the preferred side chain conformation would correspond to one of the undesired orientations S(a) or S(g–).

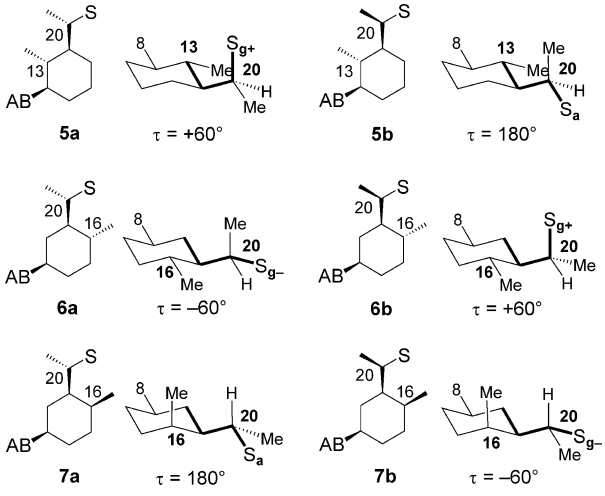
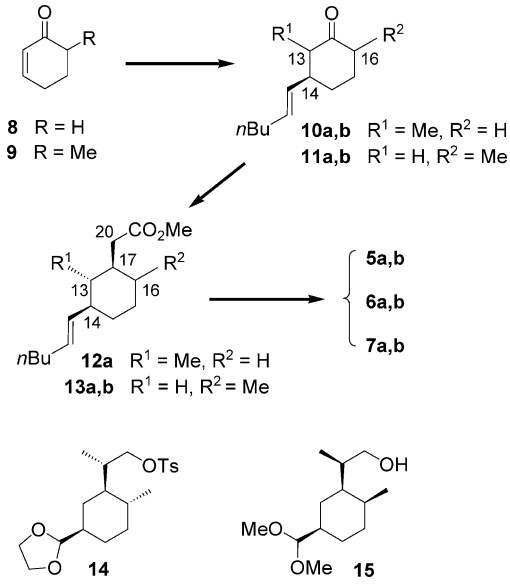


Figure 5. Biased side-chain orientations in **5a**, **5b**, **6a**, **6b**, **7a**, and **7b** with the corresponding dihedral angle value (τ) in the preferred conformation of fragment C13–C17–C20–C22 in each isomer.

Synthesis

The synthesis of analogues **5a**, **5b**, **6a**, **6b**, **7a**, and **7b** starts from conjugated cyclohexenones **8** and **9**. The general strategy is depicted in Scheme 1. In the first stage, a C13 or C16 methyl-substituted cyclohexanone (cf. **10a** and **11a**,**b**) was obtained possessing a 1-hexenyl group with the required absolute configuration at C14. In the second stage, a methoxycarbonylmethyl group was introduced at C17 with the required *cis* configuration relative to the chain at C14 to afford key intermediates **12a**, **13a**, and **13b**. In the last stage, the methoxycarbonylmethyl group was used to construct the C20 methylated analogue side chain with the required configuration **a** or **b** at C20, and the hexenyl group was oxidatively cleaved to generate an aldehyde function, which enabled the well-precedented Wittig–Horner-type coupling of the A-ring.[11]

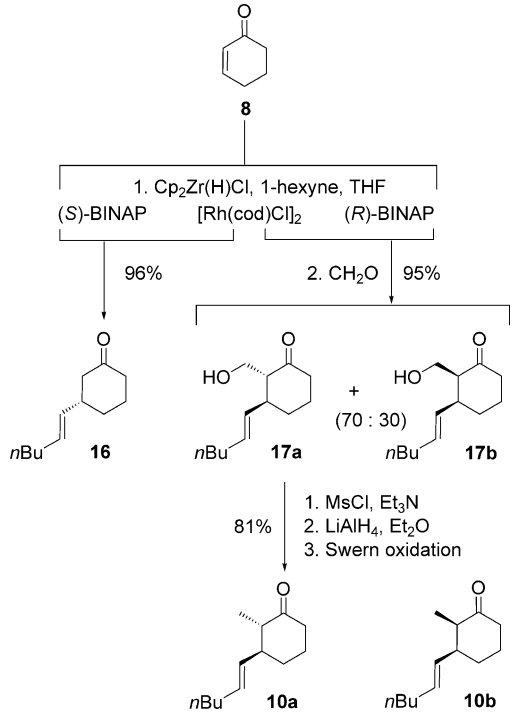
With regard to the structural determination of the different stereoisomeric intermediates that will be synthesized, it is important to note that (1) analogous stereoselectivities



Scheme 1. General synthetic strategy.

are observed in the two series that involve the all-equatorial trisubstituted intermediates **12a** (cf. analogues **5a**,**b**) and **13a** (cf. analogues **6a**,**b**) and (2) the relative configurational assignment of the stereogenic centers C14, C16, C17, and C20 in the C16-methylated series is based on the X-ray diffraction analyses of tosylate **14** (cf. analogues **6a**,**b**) and alcohol **15** (cf. analogues **7a**,**b**).

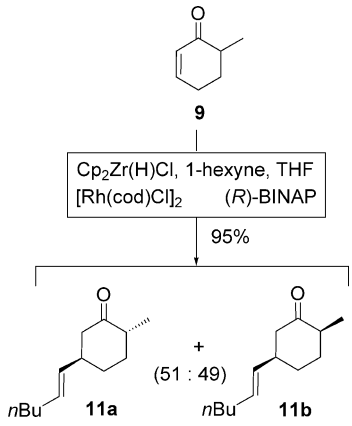
The synthesis of cyclohexanone **10a** (and **10b**) has been reported in detail and is summarized in Scheme 2.[12] It features the highly enantioselective 1,4-addition of an alkenylzirconocene chloride to 2-cyclohexenone by a chiral



Scheme 2. Enantioselective synthesis of **10a**.

rhodium(I) complex generated with BINAP as chiral ligand, a methodology which has led to the synthesis of enantiomerically pure **16**.[13] In our case, the 1,4-addition was performed by using (*E*)-1-hexenylzirconocene chloride, prepared from 1-hexyne and $Cp_2Zr(H)Cl$ (Schwartz reagent)[14] in the presence of a catalytic amount of the rhodium(I) complex $[Rh(cod)Cl]_2$ and (*R*)-BINAP, followed by trapping of the O-enolate with formaldehyde.[15] This led to a 7:3 mixture (95%) of **17a/17b** with an excellent *ee* value (better than 96%). After separation, aldol derivative **17a** was converted in good yield (81%) into required *trans*-derivative **10a**.

In a similar way, the asymmetric 1,4-addition with the use of the same catalytic conditions with (*R*)-BINAP as chiral ligand, but followed by workup with an aqueous solution of ammonium chloride, led to a 1:1 diastereomeric mixture of **11a/11b** (95% yield), which could be separated by gradient elution chromatography (Scheme 3). Again, both stereoisomers were obtained with an excellent *ee* value (better than 96%). This result further illustrates the utility of this methodology in obtaining absolute reagent stereocontrol.



Scheme 3. Enantioselective synthesis of **11a** and **11b**.

Whereas the configurational assignment of **11a** and **11b** eventually rests on their conversion into **14** and **15** (Scheme 1), respectively, the structures of which were solved by X-ray diffraction analysis, the difference between the *trans*- and *cis*-disubstituted cyclohexanones is also apparent from NMR spectroscopic analysis (Figure 6). The assignment of the *trans*-relationship in **11a** with diequatorial orientation of the alkyl substituents is in line with the axial orientation of H14, characterized by a large sum of vicinal coupling constants (37 Hz) and with the well-separated resonances of the two protons at C13 (2.44 and 1.82 ppm for the equatorial and axial hydrogen atoms, respectively). *cis*-Derivative **11b** in contrast is present as an equilibrating mixture of chair conformations, as is apparent from the protons at C13, which now resonate at δ = 2.36 and 2.12 ppm, whereas H14 possesses a much smaller sum of vicinal coupling constant values (21 Hz).

Further synthesis of key intermediates **12a**, **13a**, and **13b** from **10a**, **11a**, and **11b**, respectively, proceeds by dissolving

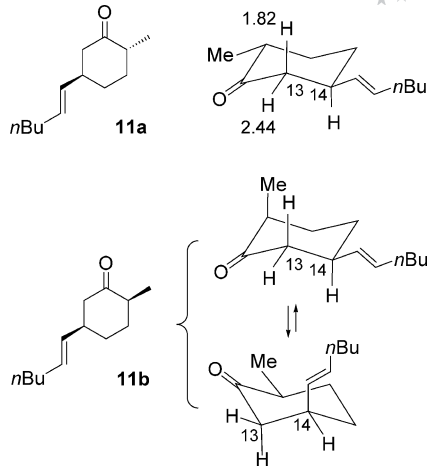
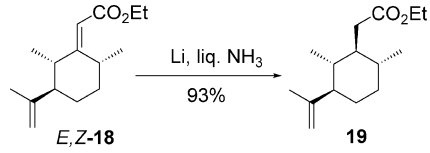


Figure 6. Conformational behavior of **11a** and **11b** with relevant ^1H NMR spectroscopic data: chemical shifts (δ) given in ppm.

metal reduction of the corresponding unsaturated esters obtained by Peterson or Horner–Wadsworth–Emmons (HWE) olefination. The choice of this methodology was dictated by prior work in which it was observed that the reduction of **18** (mixture of *E*,*Z* isomers) with lithium in liquid ammonia led to saturated ester **19** in high yield with the ethoxycarbonylmethyl side chain in the preferred equatorial orientation (Scheme 4).[10]

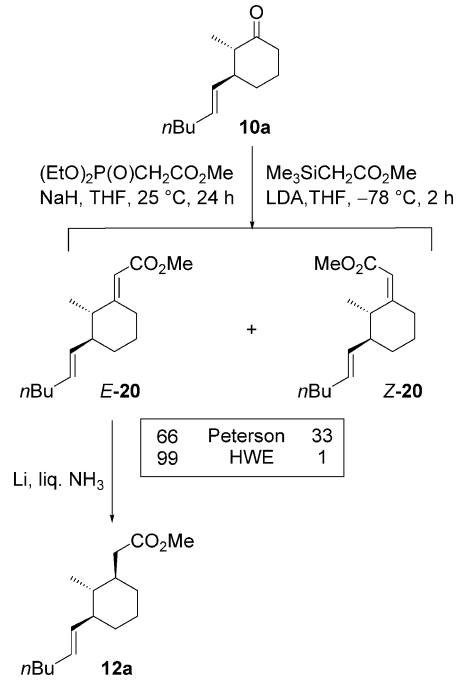


Scheme 4. Dissolving metal reduction of **18**.

Whereas the Peterson olefination of cyclohexanone **10a** led to a 2:1 mixture (98% yield) of *E*-**20**/*Z*-**20**, the HWE olefination was more stereoselective yielding the *E* isomer almost exclusively (Scheme 5). Subsequent reduction of unsaturated ester *E*-**20** with lithium in liquid ammonia at –78 °C led to saturated ester **12a** with the expected *trans* relation (80% yield). The equatorial orientation of the methoxycarbonylmethyl group is substantiated by the large sum of vicinal coupling constants of H17 (38 Hz).

The stereochemical assignment of the *E*,*Z* isomers follows from NMR spectral analysis (Figure 7). In isomer *E*-**20** with the alkyl substituents in a *trans*-equatorial orientation, the equatorial H16 is strongly deshielded (δ = 3.72 ppm); isomer *Z*-**20** in contrast adopts the conformation with the methyl group at C13 in the axial orientation (cf. nOe between methyl and H15/H16) with a deshielding of the equatorial H13 as a consequence (δ = 3.89 ppm).

As shown in Scheme 6, in a similar way cyclohexanone **11a** was subjected to the HWE conditions to afford *E* isomer *E*-**21a** almost exclusively (98% yield). Subsequent dissolving metal reduction led, under the same conditions, to the all-equatorial substituted saturated ester **13a**. Again, the Peterson olefination turned out to be much-less stereoselective and afforded a 2:1 mixture of *E*,*Z* isomers. The stereo-



Scheme 5. Synthesis of key intermediate **12a**.

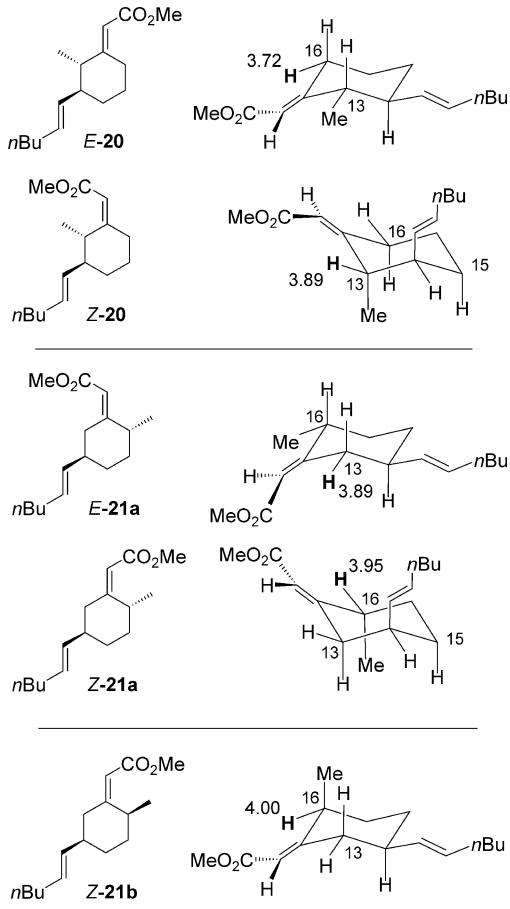
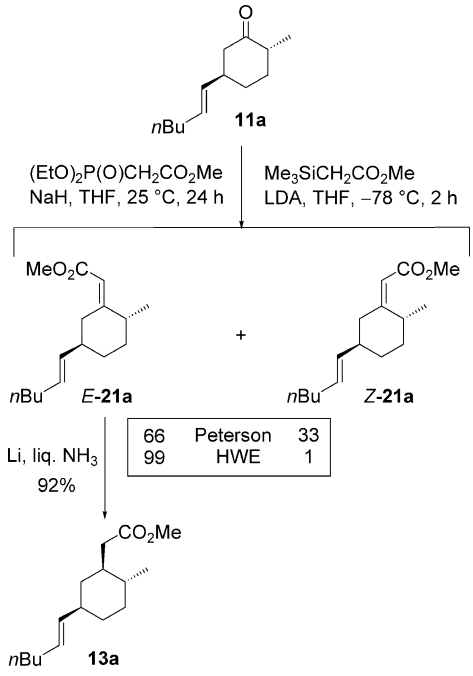


Figure 7. Conformational behavior of *E*,*Z*-**20**, *E*,*Z*-**21a**, and *Z*-**21b** with relevant ^{1}H NMR spectroscopic data: chemical shifts (δ) given in ppm.

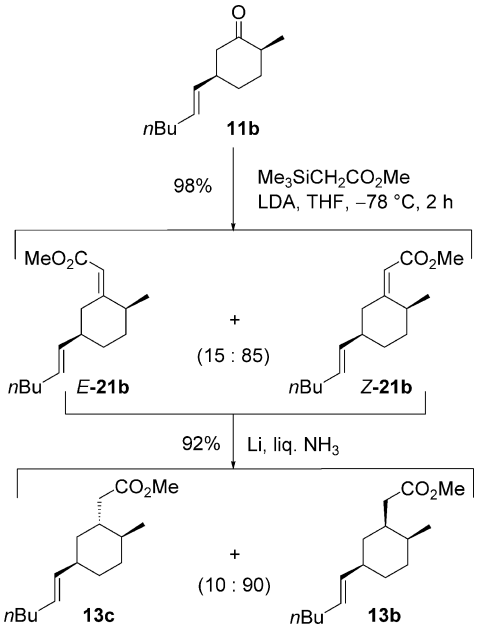
chemical assignment follows from NMR spectral analysis (Figure 7). Isomer *Z*-**21a** adopts a conformation in which both alkyl groups are axially oriented (cf. nOe between methyl and H13/H15), resulting in a strong deshielding of the equatorial H16 (δ =3.95 ppm), whereas in isomer *E*-**21a** with both alkyl substituents in a *trans*-diequatorial orientation the deshielded proton is the equatorial H13 (δ =3.89 ppm).



Scheme 6. Synthesis of key intermediate **13a**.

In the case of epimeric cyclohexanone **11b**, Peterson olefination afforded a 15:85 mixture of *E*,*Z* isomers (98% yield), which when subjected to the dissolving metal reduction conditions led to a 9:1 mixture of saturated esters **13b**/**13c** (Scheme 7). As expected, *Z*-**21b** adopts a chair conformation with the methyl group at C16 in the axial orientation with a strong deshielding of H16 (δ =4.00 ppm) as a consequence (Figure 7). The structural assignment of C17 epimeric esters **13b** and **13c** eventually rests on the obtainment of alcohol **15** in a sequence starting from major stereoisomer **13b** (Scheme 12). As mentioned earlier, the structure of **15** has been determined unambiguously by X-ray diffraction analysis. It is also interesting to note how the NMR spectroscopic data of the two protons at C20 are rather informative with respect to the configuration of saturated esters **12** and **13** (Figure 8). In fact, the same pattern is observed in all saturated esters that possess a *trans* relation between the methoxycarbonylmethyl group and the vicinal methyl substituent (i.e., **12a**, **13a**, and **13c**).

The final stage of the synthesis of the analogues required the construction of the calcitriol side chain with the stereoselective introduction of the desired C20 stereocenter that differentiates between the **a** and **b** series of analogues.[16] In this context, the synthesis of analogues **7a**,**b** proceeded through a pathway different from the one followed for the synthesis of both **5a**,**b** and **6a**,**b**. Furthermore, in the case



Scheme 7. Synthesis of key intermediate **13b**.

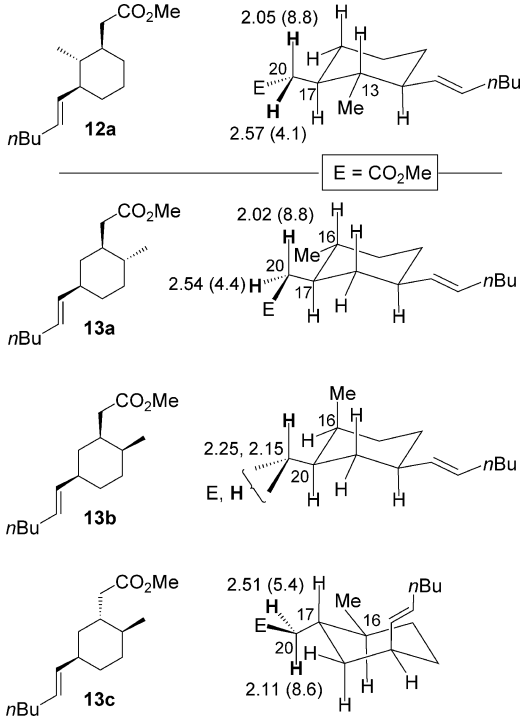
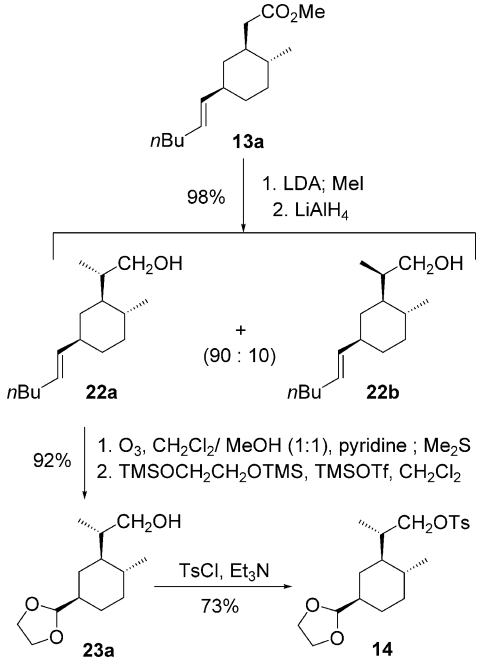


Figure 8. Conformational behavior of **12a**, **13a**, **13b**, and **13c** with relevant ^{1}H NMR spectroscopic data: chemical shifts (δ) given in ppm and vicinal coupling constant values are given in parentheses (Hz).

of analogues **5** and **6**, a different strategy was required for the stereoselective synthesis of the analogues of the **a** series compared to the analogues of the **b** series. This is due to the stereoselective outcome of the alkylation of the enolate anions derived from saturated esters **12a**, **13a**, and **13b**.

This was originally observed in an exploratory sequence that is summarized in Scheme 8. Although this sequence is slightly different from the one that was eventually adopted for the effective preparation of the analogues, there should be no relevant difference regarding the stereochemical issue. After deprotonation of saturated ester **13a** with lithium diisopropylamide (LDA), alkylation of the resulting enolate anion with iodomethane led to an inseparable mixture of stereoisomers, which was further reduced with lithium aluminum hydride to afford a 9:1 mixture of expected alcohols **22a**/**22b** (Figure 9). After separation, major isomer **22a** was converted into alcohol **23a**, the crystalline tosylate of which (**14**) was solved by X-ray diffraction analysis (Figure 10).



Scheme 8. Synthesis of tosylate **14**.

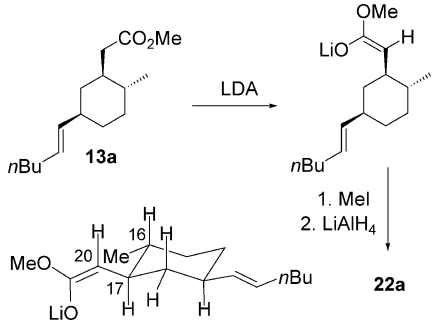


Figure 9. Origin of stereoselectivity in the alkylation at C20.

The observed high stereoselectivity in the alkylation process is in line with the expectation that the electrophile would approach the enolate anion from the least-hindered *si* face, as illustrated in Figure 9.[17] Hence by varying the nature of the electrophile (methyl iodide or propargyl bromide) as a function of the required stereochemistry at C20, it became possible to prepare analogues **5a**, **5b** and analogues **6a**, **6b** with high and predictable stereoselectivity. In the actual syntheses the hexenyl side chain is first converted into the protected aldehyde by treatment with ozone in a

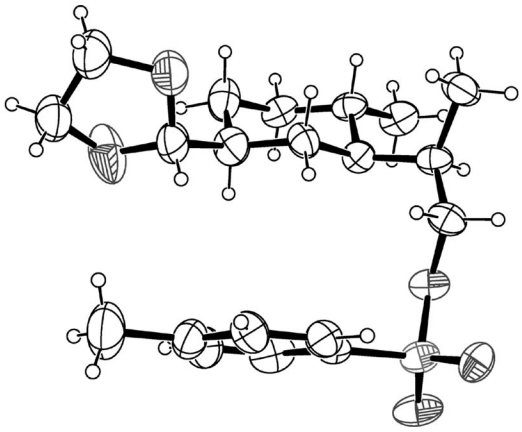
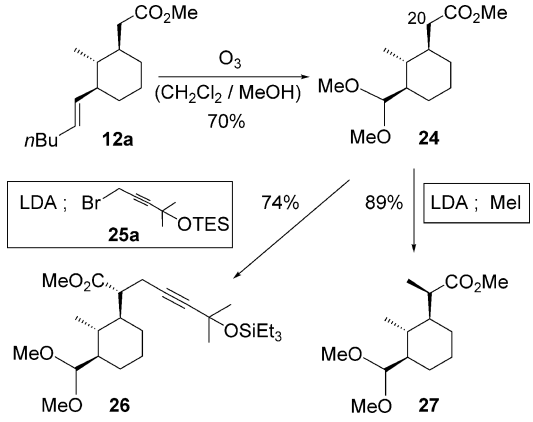


Figure 10. ORTEP structure of **14**.

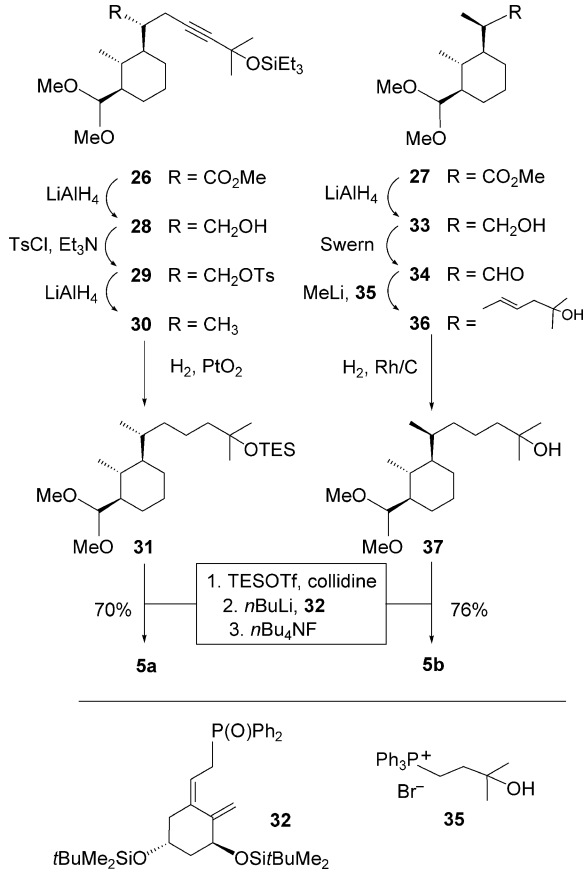
solution of dichloromethane and methanol (1:1) followed by workup with dimethyl sulfide.[18]

The synthesis of analogues **5a** and **5b** is further shown in Schemes 9 and 10. Ester **12a** was first converted into dimethyl acetal **24** (70% yield). The synthesis of analogue **5a** with the natural *R* configuration at C20 required that the enolate anion obtained from **24** be alkylated with the side chain fragment and that the ester moiety be subsequently converted into the C21 methyl group, whereas the synthesis of analogue **5b** with the *S* configuration at C20 required that the C21 methyl group be introduced by alkylation and that the ester moiety be subsequently converted into the side chain fragment. Following this strategy, the alkylation of the enolate anion derived from ester **24** with bromide **25a** led stereoselectively to alkyne **26** (74% yield), whereas the analogous alkylation with iodomethane afforded ester **27** (89%).[19]



Scheme 9. Stereoselective synthesis of intermediates **26** and **27** from ester **12a**.

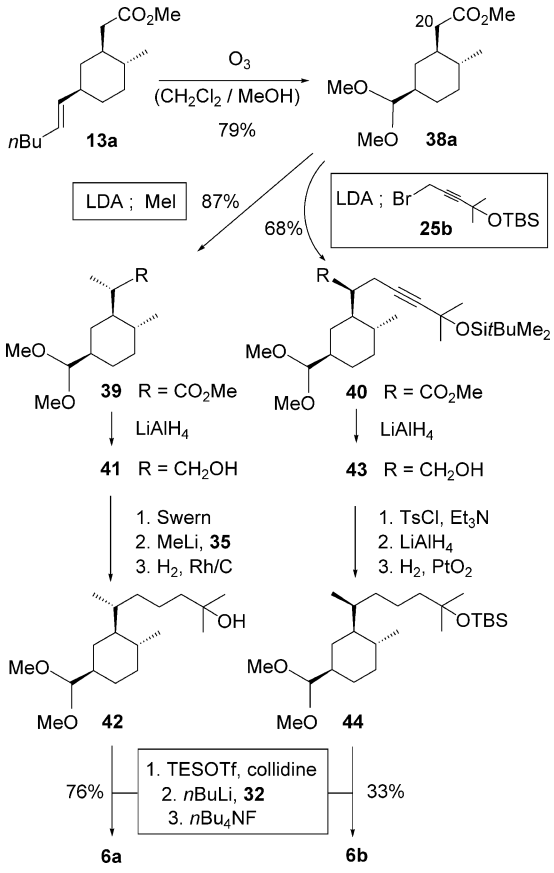
Further conversion of **26** into analogue **5a** proceeded via intermediate acetal **31** (Scheme 10). The latter was obtained following an uneventful sequence of reactions involving the reduction of ester **26** to alcohol **28**, its subsequent conversion into tosylate **29**, followed by reduction to afford the C21 methyl group in **30**. After hydrogenation of the alkyne



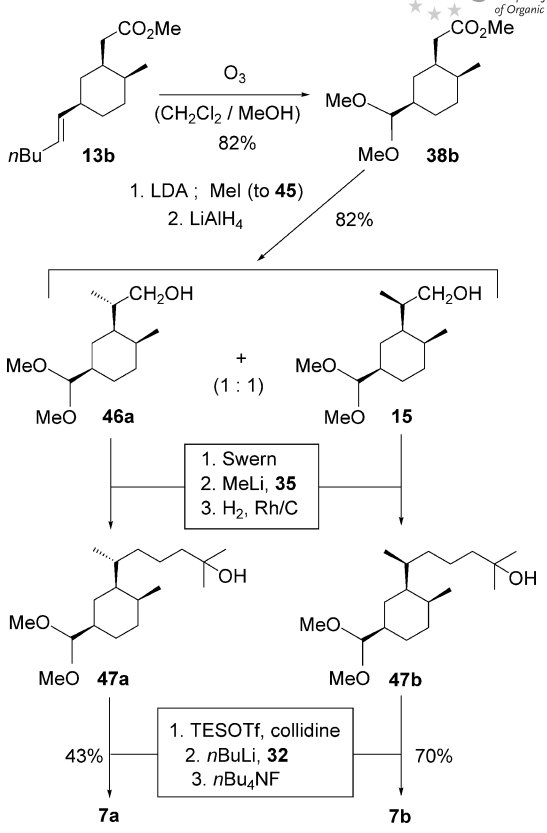
Scheme 10. Synthesis of analogues **5a** and **5b** via intermediates esters **26** and **27**.

moiety in **30**, the acetal function of intermediate **31** was hydrolyzed (triethylsilyl triflate and 2,4,6-collidine in dichloromethane),[20] and the resulting aldehyde was immediately subjected to the Wittig–Horner reaction with the anion derived from phosphane oxide **32**.[11] Desilylation finally afforded analogue **5a**. Further conversion of **27** into analogue **5b** proceeded via intermediate acetal **37** (Scheme 10). After reduction of ester **27** to alcohol **33**, followed by oxidation to aldehyde **34**, the latter was subjected to a Wittig reaction involving the ylide derived from phosphonium bromide **35**[21] to afford unsaturated side chain in **36**. After hydrogenation of the alkene moiety in **36**, the acetal function of **37** was hydrolyzed, and the obtained aldehyde was immediately converted into analogue **5b** in the same way as described for the synthesis of analogue **5a**.

As shown in Scheme 11 the synthesis of analogues **6a** and **6b** starting from ester **13a** followed the same strategy, which implied, however, that the synthesis of the analogue in the **a** series (**6a**) would proceed via ester **39**, obtained by alkylation of the enolate derived from **38a** with iodomethane, whereas the synthesis of the epimeric analogue **6b** would proceed via ester **40**, obtained through similar alkylation but involving bromide **25b** as the electrophilic reactant.



Scheme 11. Synthesis of analogues **6a** and **6b** from ester **13a**.



Scheme 12. Synthesis of analogues **7a** and **7b** from ester **13b**.

The eventual synthesis of **6a** proceeded via intermediate **42** and involved the same reaction conditions as those used for the synthesis of **5b**. The eventual synthesis of **6b** proceeded via intermediate **44** and involved the same reaction conditions as those used for the synthesis of **5a**.

As shown in Scheme 12 a different strategy was adopted for the synthesis of analogues **7a** and **7b** from ester **13b**. This originated from the observed lack of stereoselectivity in the alkylation of the enolate anion derived from **38b**. Presumably, the axial orientation of the methyl group at C16 is less efficient in the shielding of one side of the enolate anion. In practice, the alkylation with iodomethane led to a 1:1 mixture of the esters, which could not be separated at this stage. After reduction with lithium aluminum hydride the two obtained alcohols **46a** and its C20 epimer were separated by chromatography. Fortunately, 20-*epi*-**46a** was crystalline and its structure was unambiguously determined as **15** by X-ray diffraction analysis (Figure 11). After a sequence involving oxidation of alcohol **46a** to the corresponding aldehyde, Wittig coupling and hydrogenation as before, obtained acetal intermediate **47a** was subjected to the same final sequence to afford analogue **7a**. In much the same way, **7b** was obtained from alcohol **15** via acetal intermediate **47b**.

It is interesting to note that the free hydroxy group in intermediates **47** is protected as a triethylsilyl (TES) ether (cf. **48**) when the acetal deprotection conditions were applied [(i) TES triflate, 2,4,6-collidine, dichloromethane, 5 min, 0 °C; (ii) water],[20] which eventually resulted in a more-efficient subsequent Wittig–Horner coupling process (Scheme 13).

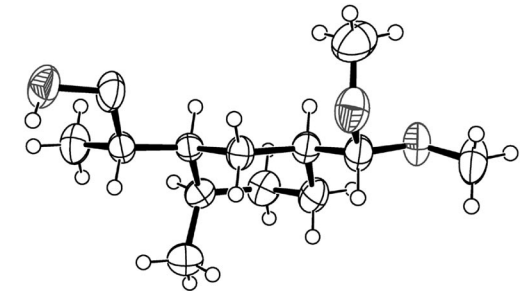
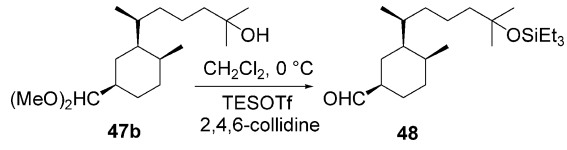


Figure 11. ORTEP structure of **15**.



Scheme 13. Hydroxysilylation in the hydrolysis of dimethylacetal **45b**.

Biological Evaluation

The biological evaluation of the analogues includes the determination of the binding affinity for the porcine intesti-

nal VDR, the antiproliferative activity in vitro on breast cancer MCF-7 cells, and the calcemic activity in vivo in vitamin D-replete normal NMRI mice. Results are shown in Table 2.

Table 2. Selected biological activities of **5**–**7**.[a]

Entry	Binding VDR (pig)	Cell proliferation MCF-7	Calcium Ca serum (mice)
1	100	100	100
5a	35	90	0.5
5b	0	0	–
6a	0	0.3	–
6b	2	90	<0.25
7a	0.3	3	–
7b	0	0	–

[a] The activities are presented as relative values; the reference value of calcitriol (**1**) is defined as 100%. Further details about the methodology are given in the Experimental Section.

6D-analogue **5a** displays 35% of the VDR affinity compared with calcitriol (100% binding). The other isomers demonstrated only 2% (**6b**) or less of the affinity for the VDR. Analogues **5a** and **6b** have equal potency to inhibit the proliferation of MCF-7 cells when compared with the activity of calcitriol, whereas the other analogues did not show any relevant antiproliferative activity. Interestingly, these two analogues have poor calcemic effects in vivo (<0.25% or less compared with calcitriol).

Conformational Analysis

Vitamin D activity is normally expressed by a genomic pathway. The hormone binds with the intracellular vitamin D receptor (VDR) so as to regulate gene transcription and synthesis of new proteins that are more directly responsible for the biological response.[22] In view of this mechanism, the geometry of the VDR–calcitriol complex is crucial. This important information has become available through the high-resolution crystal structure of the complex that shows the 3D arrangement of the ligand-binding pocket around calcitriol and reveals in particular that the elongated ligand occupies only 56% of the accessible volume of the VDR cavity.[23] In contrast, in studies dealing with structure–activity relationships related to the orientation of the side chain, a few regions were identified in which the preferred orientation of the 25-hydroxy group would correspond to an increased cell-differentiating potency.[8] Interestingly, these do not correspond directly with the position of the 25-hydroxy group in the VDR-calcitriol complex.

Central in this and related work is the use of conformational maps to describe the preferred geometries of the side chain. The concept of dot maps in this area was first introduced by Okamura and Midland.[24] In this approach, force-field calculations are performed so as to generate within a given energy window (usually 20 kJ mol^{-1}) all possible local minimum energy conformations that the side chain may adopt. The orientation in space of each found conformation is defined by a dot that corresponds to the position of the 25-oxygen atom in that particular conformation. Subsequently, volume maps have been used in our group to optimize visualization.[25] Volume maps corresponding to the side-chain conformations of **5a/5b**, **6a/6b**, and **7a/7b** are shown in Figure 12. To a reasonable extent, these correspond nicely with the preferred conformations that were presented in Figure 5.

In Figure 12 is also shown a section of a spherical region that we have defined previously as the relative activity volume.[25] The latter is generated so that, among a pair of epimeric analogues possessing very different activities (ideally a very active and an inactive compound), a sphere is created that contains the lowest possible mol fraction of the side-chain conformations of the less-active analogue, but at the same time contains the highest possible mol fraction of the conformations of the more active of the pair. The section of this volume that is shown as a green circle in the Figure 12 was originally generated on the basis of the conformational profiles of the most- and least-active stereoiso-

Figure 12. Volume maps representing the conformational behavior of the side chain of analogues **5**, **6**, and **7** in which the AB portion has been deleted with inclusion of a section of the relative activity volume; front view. The position of O25 in receptor-bound conformation (black dot) is taken from ref.[23] Left: **5a** (green) and **5b** (pink); middle: **6a** (green) and **6b** (pink); right: **7a** (green) and **7b** (pink).

mers among four 22-methyl-substituted analogues described by Yamada.[26] The occupation of this volume by the 25-hydroxy group of the side chain was calculated to correspond to 66, 1, 2, 67, 5, and 9% for **5a**, **5b**, **6a**, **6b**, **7a**, and **7b**, respectively. As was the case for the three isomeric 6D-analogues **4a**, **4b**, and **4c**,[10] a very nice correlation is observed also for the 6D-analogues in the **5**, **6**, and **7** series between the calculated occupancies and the biological activity, at least with respect to the antiproliferative activity. This is however not reflected when comparing the binding affinities for the nuclear VDR, in particular when comparing the two active compounds **5a** and **6b**. Presumably, the unnatural location of the C16 methyl group is responsible for the observed loss in affinity.

Conclusions

Six 6D-analogues **5a**, **5b**, **6a**, **6b**, **7a**, and **7b** possessing biased side-chain conformations were synthesized and their biological activities evaluated. In this way a study is rounded in which a series of 6D-analogues was conceived featuring a dimethyl substitution pattern among three positions (i.e., C13, C16, and C20), the relative locations and stereogenicities of which are determining for the orientation of the side chain. The present study further confirms that there exists a relationship between the preferred orientation of the side chain and the antiproliferative activity of the analogues that is not necessarily reflected in the measured binding affinities for the nuclear vitamin D receptor.

Experimental Section

(2*R*,5*R*)-5-[(*E*)-Hex-1-enyl]-2-methylcylohexanone (11a) and (2*S*,5*R*)-5-[(*E*)-hex-1-enyl]-2-methylcylohexanone (11b): To a solution of $Cp_2Zr(H)Cl$ (1.2 equiv.) in tetrahydrofuran (0.3 M) was added 1-hexyne (1.2 equiv.), and the resulting mixture was stirred at room temperature for 45 min. A solution of $[Rh(cod)Cl]_2$ (5 mol-%) and (*R*)-BINAP (6 mol-%) in tetrahydrofuran (0.05 M) in a two-necked flask was stirred for 30 min at 20 °C. To this Rh solution was first added 6-methyl-2-cyclohexenone (**9**; 2.57 g, 25 mmol, 1 equiv.), followed by the addition of the Zr solution by a double tipped needle, and the resulting mixture was further stirred at room temperature for 3 h. After addition of an aqueous solution of ammonium chloride (2 M) and *tert*-butyl methyl ether (2 times the volume of tetrahydrofuran), the precipitate was filtered through a short pad of Celite and silica gel. The organic phase was separated, dried (magnesium sulfate), and concentrated in vacuo. The resulting 1:1 mixture of cyclohexanones **11a** and **11b** (4.62 g, 95% yield) was purified by column chromatography involving gradient elution with pentane/ethyl acetate (from 87:13 to 75:25). The *ee* (better than 96% for both derivatives) was determined by chiral HPLC (Daicel CHIRALPAK; *n*-hexane/ethanol, 99:1). Data for **11a**: R_f = 0.43 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = +16.0 (*c* = 1.1, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 5.24 (dtd, *J* = 15.3, 6.6, 0.8 Hz, 1 H), 5.17 (dd, *J* = 15.3, 6.4 Hz, 1 H), 2.44 (ddd, *J* = 13.0, 4.1, 2.2 Hz, 1 H), 2.10 (m, 1 H), 1.92 (q, *J* = 7.0 Hz, 2 H), 1.82 (m, 2 H), 1.60 (m, 1 H), 1.52 (m, 1 H), 1.26 (m, 4 H), 1.13 (qd, *J* = 13.2, 3.5 Hz, 1 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 1.02 (qd, *J* = 13.1, 3.3 Hz, 1 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 209.5 (C=O), 133.9 (=CH), 129.3 (=CH), 48.1 (CH_2), 44.4 (CH), 43.1 (CH), 34.8 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 22.5 (CH_2), 14.8 (CH_3), 14.1 (CH_3) ppm. IR: $\tilde{\nu}$ = 2957 (s), 2928 (vs), 2856 (s), 1714 (vs), 1457 (w), 1377 (vw), 1317 (vw), 1216 (vw), 1950 (vw), 968 (w) cm^{-1}. MS: *m*/*z* (%) = 193 (5), 165 (5), 151 (12), 137 (26), 124 (75), 109 (48), 95 (38), 81 (73), 67 (64), 55 (53), 41 (100). Data for **11b**: R_f = 0.44 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = +20.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 5.41 (dtd, *J* = 15.5, 6.7, 1.4 Hz, 1 H), 5.27 (ddt, *J* = 15.5, 5.9, 1.3 Hz, 1 H), 2.45 (m, 1 H), 2.36 (ddd, *J* = 13.8, 4.9, 1.4 Hz, 1 H), 2.12 (ddd, *J* = 13, 5.7, 1.4 Hz, 1 H), 1.97 (m, 1 H), 1.45 (m, 4 H), 1.24 (m, 4 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.84 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 210.4 (C=O), 132.5 (=CH), 131.3 (=CH), 45.2 (CH_2), 44.8 (CH), 39.7 (CH), 32.7 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 22.2 (CH_2), 15.3 (CH_3), 14.1 (CH_3) ppm. IR: $\tilde{\nu}$ = 2958 (s), 2927 (vs), 2857 (m), 1712 (vs), 1670 (vw), 1457 (m), 1376 (w), 1216 (w), 1147 (vw), 1120 (vw), 1070 (w), 981 (w) cm^{-1}. MS: *m*/*z* (%) = 193 (7), 165 (6), 151 (16), 137 (36), 124 (97), 109 (58), 95 (45), 67 (70), 55 (59), 41 (100).

Representative Procedure for the Horner–Wadsworth–Emmons Olefination involving Cyclohexanones 10a and 11a: To a cooled (–20 °C) suspension of sodium hydride (4 equiv.) in tetrahydrofuran (0.7 M) was added $(EtO)_2P(O)CH_2CO_2Me$ (4 equiv.). After stirring for 30 min, the reaction mixture was brought to room temperature and further stirred for 1 h. To the cooled (0 °C) mixture was added a solution of ketone (1 equiv.) in tetrahydrofuran (0.7 M). After stirring overnight at room temperature a saturated solution of sodium hydrogen carbonate was added, and the mixture was extracted with *tert*-butyl methyl ether. The combined organic phase was dried (magnesium sulfate) and further concentrated in vacuo. The residue was further purified by column chromatography with pentane/ethyl acetate (98.5:1.5). From **10a** (2.91 g, 15 mmol) was obtained 3.68 g of *E*-**20** (98%) and from **11a** (3.08 g, 15.9 mmol) 3.90 g of *E*-**21a** (98%).

***E*-20:** R_f = 0.62 (*i*-octane/EtOAc, 6:4). $[\alpha]_D$ = –131.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.61 (s, 1 H), 5.37 (dt, *J* = 15.1, 6.6 Hz, 1 H), 5.26 (dd, *J* = 15.1, 8.5 Hz, 1 H), 3.71 (m, 1 H), 3.69 (s, 3 H), 1.98 (m, 4 H), 1.87 (m, 1 H), 1.78 (m, 1 H), 1.73 (m, 1 H), 1.41 (m, 2 H), 1.31 (m, 4 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7 (C=O), 166.7 (=C), 134.2 (=CH), 130.7 (=CH), 110.9 (=CH), 50.8 (OCH_3), 50.7 (CH), 44.3 (CH), 33.1 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 30.0 (CH_2), 26.9 (CH_2), 22.2 (CH_2), 16.3 (CH_3), 13.9 (CH_3) ppm. IR: $\tilde{\nu}$ = 2929 (vs), 2862 (s), 1719 (vs), 1645 (s), 1442 (m), 1380 (w), 1308 (w), 1164 (vs), 974 (w) cm^{-1}. MS: *m*/*z* (%) = 250 (5) [M^+], 221 (10), 219 (10), 191 (39), 179 (5), 165 (12), 152 (14), 133 (12), 121 (18), 119 (13), 105 (19), 91 (32), 81 (49), 67 (76), 55 (41), 41 (100). $C_{16}H_{26}O_2$ (250.38): calcd. C 76.75, H 10.47; found C 76.12, H 10.32.

***E*-21a:** R_f = 0.64 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = –21.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.63 (s, 1 H), 5.49 (dt, *J* = 15.5, 6.0 Hz, 1 H), 5.43 (dd, *J* = 15.5, 6.0 Hz, 1 H), 3.89 (ddd, *J* = 12.7, 3.3, 1.8 Hz, 1 H), 3.69 (s, 3 H), 2.12 (m, 1 H), 2.07 (m, 1 H), 1.97 (m, 2 H), 1.91 (dq, *J* = 12.9, 3.7 Hz, 1 H), 1.78 (m, 1 H), 1.63 (t, *J* = 12.7 Hz, 1 H), 1.34 (qd, *J* = 12.9, 3.8 Hz, 1 H), 1.30 (m, 4 H), 1.15 (qd, *J* = 12.9, 3.8 Hz, 1 H), 1.04 (d, *J* = 6.5 Hz, 3 H, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6 (C=), 166.2 (C=O), 134.5 (=CH), 129.0 (=CH), 110.4 (=CH), 50.9 (OCH_3), 42.7 (CH), 39.4 (CH), 36.6 (CH_2), 36.5 (CH_2), 32.9 (CH_2), 32.3 (CH_2), 31.7 (CH_2), 22.2 (CH_2), 18.0 (CH_3), 14.0 (CH_3) ppm. IR: $\tilde{\nu}$ = 2957 (s), 2926 (vs), 2854 (s), 1721 (vs), 1647 (m), 1458 (m), 1434 (m), 1387 (w), 1336 (w), 1234 (m), 1191

(m), 1161 (m), 1013 (w) cm^{-1}. MS: *m*/*z* (%) = 250 (28), 219 (13), 191 (17), 161 (18), 147 (11), 133 (14), 119 (17), 107 (22), 105 (23), 91 (34), 81 (35), 67 (56), 55 (44), 41 (100).

Representative Procedure for the Peterson Olefination involving Cyclohexanones 10a, 11a, and 11b: To a cooled solution of lithium diisopropylamide (1.2 equiv.) in tetrahydrofuran obtained by addition of *n*-butyllithium (2.5 M in *n*-hexane, 1.2 equiv.) to a solution of diisopropylamine (1.2 equiv.) in tetrahydrofuran (0.5) was added $TMSCH_2COOMe$ (1.2 equiv.) dropwise at –78 °C. After stirring at –78 °C for 30 min, the ketone (1.2 equiv.) was added. The resulting mixture was stirred for 1 h at –78 °C, and subsequently for another 1 h at 20 °C. After addition of a saturated solution of ammonium chloride and extraction with *tert*-butyl methyl ether, the organic phase was dried (magnesium sulfate) and concentrated in vacuo. The mixture of esters was further separated by column chromatography with pentane/ethyl acetate (98:2). In the case of **10a** (1.75 g, 9 mmol) a 2:1 mixture of *E*,*Z*-**20** was obtained (2.21 g, 98% yield); in the case of **11a** (0.972 g, 5 mmol) a 2:1 mixture of *E*,*Z*-**21a** (1.23 g, 98% yield). In the case of **11b** (3.87 g, 20 mmol) a 15:85 mixture of *E*-**21b** and *Z*-**21b** (4.91 g, 98% yield) was obtained, which was not separated by chromatography but directly subjected to dissolving metal reduction.

***Z*-20:** R_f = 0.50 (*i*-octane/EtOAc, 8:2). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.64 (d, *J* = 1.7 Hz, 1 H), 5.40 (m, 2 H), 3.89 (td, *J* = 7.2, 2.4 Hz, 1 H), 3.68 (s, 3 H), 2.39 (m, 1 H), 2.27 (m, 1 H), 2.04 (m, 1 H), 1.96 (m, 2 H), 1.86 (m, 1 H), 1.64 (m, 2 H), 1.43 (m, 1 H), 1.29 (m, 4 H), 1.19 (d, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7 (C=O), 166.5 (=C), 133.2 (=CH), 130.7 (=CH), 114.2 (=CH), 50.9 (OCH_3), 44.3 (CH), 36.1 (CH), 33.2 (CH_2), 32.7 (CH_2), 26.0 (CH_2), 22.6 (CH_2), 22.1 (CH_2), 19.1 (CH_3), 16.8 (CH_3) ppm. IR: $\tilde{\nu}$ = 2932 (vs), 2871 (s), 1718 (vs), 1642 (s), 1458 (m), 1435 (s), 1385 (m), 1220 (s), 1162 (vs), 1122 (w), 1024 (m), 968 (m), 915 (m) cm^{-1}. MS: *m*/*z* (%) = 250 (36) [M^+], 221 (24), 191 (95), 179 (14), 165 (26), 152 (20), 139 (39), 133 (35), 121 (44), 105 (50), 91 (62), 79 (76), 67 (100), 55 (58).

***Z*-21a:** R_f = 0.64 (*i*-octane/EtOAc, 8:2). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.55 (d, *J* = 1.8 Hz, 1 H), 5.41 (m, 2 H), 3.95 (m, 1 H), 3.67 (s, 3 H), 3.65 (ddd, *J* = 13.8, 5.7, 1.8 Hz, 1 H), 2.58 (m, 1 H), 2.00 (m, 1 H), 1.96 (m, 2 H), 1.92 (m, 1 H), 1.78 (m, 1 H), 1.40 (m, 1 H), 1.37 (m, 1 H), 1.28 (m, 4 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5 (C=), 165.8 (C=O), 132.0 (=CH), 130.4 (=CH), 114.1 (=CH), 50.6 (OCH_3), 38.1 (CH), 37.6 (CH), 32.1 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 27.5 (CH_2), 25.7 (CH_2), 22.0 (CH_2), 18.5 (CH_3), 13.8 (CH_3) ppm. IR: $\tilde{\nu}$ = 2956 (s), 2928 (vs), 2857 (m), 1720 (vs), 1646 (m), 1459 (m), 1434 (m), 1386 (w), 1368 (w), 1233 (s), 1191 (m), 1160 (vs), 1144 (m) cm^{-1}. MS: *m*/*z* (%) = 250 (27), 219 (10), 191 (19), 165 (21), 147 (11), 133 (17), 119 (17), 107 (23), 105 (23), 91 (31), 81 (38), 67 (55), 55 (44), 41 (100).

***Z*-21b:** R_f = 0.50 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = –4.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.56 (d, *J* = 1.5 Hz, 1 H), 5.40 (dt, *J* = 15.4, 5.7 Hz, 1 H), 5.34 (dd, *J* = 15.4, 5.4 Hz, 1 H), 4.00 (m, 1 H), 3.66 (s, 3 H), 2.20 (td, *J* = 13.4, 1.5 Hz, 1 H), 2.05 (m, 1 H), 2.02 (m, 1 H), 1.96 (m, 2 H), 1.55 (m, 2 H), 1.50 (m, 2 H), 1.30 (m, 4 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.96 (C=), 166.89 (C=O), 134.05 (=CH), 129.03 (=CH), 112.97 (=CH), 50.80 (CH_3), 43.80 (CH), 39.50 (CH), 32.25 (CH_2), 32.18 (CH_2), 32.72 (CH_2), 30.07 (CH_2), 27.16 (CH_2), 22.19 (CH_2), 18.29 (CH_3), 13.97 (CH_3) ppm. IR: $\tilde{\nu}$ = 2954 (m), 2926 (s), 2855 (m), 1720 (vs), 1644 (m), 1463 (w), 1433 (m), 1385 (w), 1367 (vw), 1242 (m), 1191 (m), 1153 (vs), 1023 (w), 854 (vw) cm^{-1}. MS: *m*/*z* (%) = 250 (59) [M^+], 235 (3), 219 (12), 207 (5), 191 (35), 179 (12), 165 (30), 161 (15), 147 (17), 133 (28), 119 (32), 107 (32), 105 (36), 93 (41), 79 (46), 67 (63), 55 (39), 41 (100).

Representative Procedure for the Dissolving Metal Reduction with Lithium in Liquid Ammonia involving Unsaturated Esters *E*-20 and *E*-21a and the Mixture *E*,*Z*-21b: To a solution of lithium (2.5 equiv.) in liquid ammonia was added at –75 °C a solution of the unsaturated ester (1 equiv.) in diethyl ether (0.2 M). After stirring for 45 min at –60 °C 2-bromo-2-methylpropane was added until appearance of the red color of triphenyllithium. After addition of ammonium chloride, *tert*-butyl methyl ether was added to the white suspension and the ammonia gas was allowed to evaporate. The resulting suspension was filtered through a short pad of silica gel. After concentration of the filtrate in vacuo, the residue was purified by column chromatography with pentane/ethyl acetate (99:1) followed by HPLC with cyclohexane/*tert*-butyl methyl ether (99.5:0.5) to yield the saturated ester as an oil. The reduction of *E*-**20** (3.08 g, 12.3 mmol) and *E*-**21a** (2.0 g, 7.99 mmol) gave **12a** (2.48 g, 80% yield) and **13a** (1.86 g, 92% yield), respectively. In the case of *E*,*Z*-**21b** (1.95 g, 7.8 mmol) purification of the reaction mixture led to a 9:1 mixture (1.50 g, 76% yield) of **13b** and **13c**.

12a: R_f = 0.60 (*i*-octane/EtOAc, 6:4). $[\alpha]_D$ = –14.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.35 (dt, *J* = 15.1, 6.6 Hz, 1 H), 5.14 (dd, *J* = 15.1, 8.5 Hz, 1 H), 3.66 (s, 3 H), 2.57 (dd, *J* = 14.8, 4.1 Hz, 1 H), 2.03 (dd, *J* = 14.8, 8.8 Hz, 1 H), 1.97 (m, 2 H), 1.69 (m, 2 H), 1.60 (m, 2 H), 1.48 (m, 1 H), 1.31 (m, 5 H), 1.11 (qd, *J* = 12.9, 2.8 Hz, 1 H), 1.03 (m, 1 H), 0.88 (m, 7 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1 (C=O), 135.3 (=CH), 130.1 (=CH), 51.4 (OCH_3), 48.6 (CH), 41.2 (CH), 41.0 (CH), 39.6 (CH_2), 34.1 (CH_2), 32.7 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 22.2 (CH_2), 17.4 (CH_3), 13.9 (CH_3) ppm. IR: $\tilde{\nu}$ = 2957 (s), 2924 (vs), 2854 (s), 1741 (vs), 1458 (m), 1438 (m), 1338 (w), 1247 (w), 1194 (m), 1169 (m), 1131 (m), 969 (m) cm^{-1}. MS: *m*/*z* (%) = 252 (12) [M^+], 221 (8), 192 (8), 178 (51), 167 (19), 149 (12), 136 (21), 121 (25), 108 (80), 95 (43), 81 (41), 79 (40), 67 (51), 55 (56), 41 (100). $C_{16}H_{28}O_2$ (252.38): calcd. C 76.14, H 11.18; found C 74.67, H 10.94.

13a: R_f = 0.49 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = +1.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.46 (dd, *J* = 15.6, 5.7 Hz, 1 H), 5.40 (dt, *J* = 15.6, 5.8 Hz, 1 H), 3.66 (s, 3 H), 2.51 (dd, *J* = 14.8, 5.4 Hz, 1 H), 2.34 (m, 1 H), 2.11 (dd, *J* = 14.8, 8.6 Hz, 1 H), 2.0 (m, 2 H), 1.79 (m, 1 H), 1.64 (dt, *J* = 13.4, 4.7 Hz, 1 H), 1.45–1.57 (m, 3 H), 1.24–1.36 (m, 7 H), 0.93 (d, *J* = 6.2 Hz, 3 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0 (C=O), 133.9 (=CH), 129.5 (=CH), 51.4 (OCH_3), 39.2 (CH_2), 36.2 (CH), 35.7 (CH), 35.5 (CH_2), 35.5 (CH), 32.7 (CH_2), 32.3 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 22.2 (CH_2), 19.8 (CH_3), 14.0 (CH_3) ppm. IR: $\tilde{\nu}$ = 2955 (s), 2923 (vs), 2855 (s), 1741 (vs), 1458 (m), 1436 (m), 1377 (w), 1343 (w), 1283 (w), 1160 (m), 968 (m) cm^{-1}. MS: *m*/*z* (%) = 252 (42) [M^+], 220 (19), 203 (7), 192 (33), 178 (99), 163 (12), 149 (39), 135 (21), 121 (39), 108 (43), 93 (61), 79 (44), 67 (43), 55 (49), 41 (100).

13b: R_f = 0.46 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = –3.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.36 (dt, *J* = 15.5, 6.1 Hz, 1 H), 5.31 (dd, *J* = 15.5, 5.7 Hz, 1 H), 3.67 (s, 3 H), 2.25 (dd, *J* = 14.6, 6.9 Hz, 1 H), 2.15 (dd, *J* = 14.6, 7.9 Hz, 1 H), 2.05 (m, 1 H), 1.96 (m, 2 H), 1.92 (m, 1 H), 1.84 (m, 1 H), 1.57 (m, 2 H), 1.44 (m, 2 H), 1.30 (m, 4 H), 1.20 (m, 1 H), 1.03 (m, 1 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.78 (C=O), 135.65 (=CH), 128.13 (=CH), 51.43 (OCH_3), 40.92 (CH), 39.47 (CH_2), 37.28 (CH), 33.12 (CH_2), 32.94 (CH_2), 32.31 (CH_2), 31.83 (CH_2), 30.60 (CH), 26.58 (CH_2), 22.20 (CH_2), 13.98 (CH_3), 11.90 (CH_3) ppm. IR: $\tilde{\nu}$ = 2957 (s), 2922 (vs), 2854

(s), 1741 (vs), 1465 (w), 1436 (m), 1381 (w), 1253 (w), 1193 (m), 1174 (m), 1124 (w), 997 (vw), 968 (m) cm^{-1}. MS: *m*/*z* (%) = 252 (43) [M^+], 221 (26), 193 (51), 178 (69), 149 (39), 135 (28), 121 (42), 108 (79), 93 (63), 79 (50), 67 (46), 55 (46), 41 (100).

13c: R_f = 0.49 (*i*-octane/EtOAc, 8:2). $[\alpha]_D$ = +1.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.46 (dd, *J* = 15.6, 5.7 Hz, 1 H), 5.40 (dt, *J* = 15.6, 5.8 Hz, 1 H), 3.66 (s, 3 H), 2.51 (dd, *J* = 14.8, 5.4 Hz, 1 H), 2.34 (m, 1 H), 2.11 (dd, *J* = 14.8, 8.6 Hz, 1 H), 2.00 (m, 2 H), 1.79 (m, 1 H), 1.64 (dt, *J* = 13.4, 4.7 Hz, 1 H), 1.45–1.57 (m, 3 H), 1.47 (m, 3 H), 1.24–1.36 (m, 7 H), 0.93 (d, *J* = 6.2 Hz, 3 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.0 (C=O), 133.9 (=CH), 129.5 (=CH), 51.4 (OCH_3), 39.2 (CH_2), 36.2 (CH), 35.7 (CH), 35.5 (CH_2), 35.5 (CH), 32.7 (CH_2), 32.3 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 22.2 (CH_2), 19.8 (CH_3), 14.00 (CH_3) ppm. IR: $\tilde{\nu}$ = 2955 (s), 2923 (s), 2855 (s), 1741 (vs), 1458 (m), 1436 (m), 1377 (w), 1343 (w), 1256 (m), 1193 (s), 1158 (s), 1134 (s), 1055 (s), 966 (w) cm^{-1}. MS: *m*/*z* (%) = 212 (25), 181 (8), 138 (100), 123 (44), 106 (45), 91 (28), 74 (22), 67 (14), 55 (25), 41 (42).

Representative Procedure for the Oxidative Cleavage of the Hexenyl Side Chain in Esters 12a, 13a and 13b: To a cooled (–40 °C) solution of the alkene (1 equiv.) in dichloromethane/methanol (1:1, 0.1 M) was passed a stream of ozone until appearance of a light-blue color. A stream of nitrogen was subsequently led through the solution until disappearance of the blue color, and the temperature was raised to –20 °C. After addition of dimethyl sulfide (5 equiv.) and overnight stirring at room temperature, a saturated solution of sodium hydrogen carbonate was added, and the resulting mixture was partly concentrated in vacuo. The aqueous phase was further extracted with *tert*-butyl methyl ether, and the resulting organic phase was dried (magnesium sulfate). After concentration in vacuo, the residue was purified by column chromatography with pentane/ethyl acetate (9:1) to afford the pure acetals. From **12a** (0.61 g, 2.4 mmol) was obtained 0.41 g of **24** (70% yield), from **13a** (1.15 g, 4.6 mmol) 0.87 g of **38a** (79% yield), and from **13b** (1.34 g, 5.29 mmol) 1.06 g of **38b** (82% yield).

24: R_f = 0.44 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = –4.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, *J* = 2.5 Hz, 1 H), 3.66 (s, 3 H), 3.43 (s, 3 H), 3.39 (s, 3 H), 2.58 (dd, *J* = 14.8, 4.1 Hz, 1 H), 2.02 (dd, *J* = 14.8, 8.8 Hz, 1 H), 1.80 (m, 1 H), 1.75 (m, 1 H), 1.69 (m, 1 H), 1.60 (m, 1 H), 1.33 (m, 1 H), 1.19 (m, 3 H), 1.02 (qd, *J* = 12.4, 3.5 Hz, 1 H), 0.96 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2 (C=O), 107.8 (CH), 56.8 (OCH_3), 56.0 (OCH_3), 51.4 (OCH_3), 47.0 (CH), 41.0 (CH), 39.5 (CH_2), 37.6 (CH), 32.8 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 16.2 (CH_3) ppm. IR: $\tilde{\nu}$ = 2931 (s), 2858 (m), 1737 (vs), 1440 (m), 1372 (m), 1293 (w), 1252 (m), 1198 (m), 1168 (m), 1121 (s), 1075 (s), 1019 (w), 961 (w) cm^{-1}. MS: *m*/*z* (%) = 243 [M^+], 118 (4), 149 (3), 138 (5), 121 (4), 107 (9), 95 (8), 79 (8), 75 (100), 59 (11), 47 (17), 41 (15). $C_{13}H_{24}O_4$ (244.32): calcd. C 63.91, H 9.90; found C 63.38, H 9.76.

38a: R_f = 0.53 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = –28.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (d, *J* = 7.0 Hz, 1 H), 3.65 (s, 3 H), 3.31 (s, 6 H), 2.53 (dd, *J* = 15.1, 4.4 Hz, 1 H), 2.05 (dd, *J* = 15.1, 8.8 Hz, 1 H), 1.77 (m, 1 H), 1.73 (m, 2 H), 1.65 (m, 1 H), 1.45 (m, 1 H), 1.07 (m, 1 H), 1.02 (m, 2 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 0.82 (q, *J* = 12.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9 (C=O), 108.4 (CH), 53.7 (2 × OCH_3), 51.4 (OCH_3), 40.6 (CH), 40.1 (CH), 39.3 (CH_2), 37.0 (CH), 34.9 (CH_2), 34.0 (CH_2), 27.6 (CH_2), 19.8 (CH_3) ppm. IR: $\tilde{\nu}$ = 2949 (m), 2917 (m), 2849 (m), 1735 (vs), 1437 (m), 1369 (w), 1347 (w), 1273 (w), 1222 (m), 1195 (m), 1162 (s), 1132 (vs), 1092 (s), 1076 (s), 1054 (vs), 957 (m), 903 (w), 704 (vw) cm^{-1}. MS: *m*/*z* (%) = 209 (1), 181 (1), 169 (3), 149 (3), 124 (2), 107 (6), 95 (5), 75 (100), 67 (12), 51 (10).

38b: R_f = 0.55 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = +8.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.99 (d, *J* = 6.8 Hz, 1 H), 3.66 (s, 3 H), 3.32 (s, 6 H), 2.23 (dd, *J* = 14.8, 7.7 Hz, 1 H), 2.15 (dd, *J* = 14.8, 7.3 Hz, 1 H), 2.01 (m, 1 H), 1.84 (m, 1 H), 1.67 (m, 1 H), 1.56 (m, 2 H), 1.49 (m, 2 H), 1.16 (m, 1 H), 0.97 (q, *J* = 12.6 Hz, 1 H), 0.81 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6 (C=O), 108.4 (CH), 53.7 (OCH_3), 51.5 (2 × OCH_3), 40.4 (CH), 39.4 (CH_2), 36.9 (CH), 32.5 (CH_2), 30.6 (CH), 27.7 (CH_2), 21.2 (CH_2), 11.8 (CH_3) ppm. IR: $\tilde{\nu}$ = 2948 (s), 2830 (w), 1738 (vs), 1456 (w), 1440 (m), 1382 (w), 1256 (m), 1193 (s), 1158 (s), 1134 (s), 1055 (s), 966 (w) cm^{-1}. MS: *m*/*z* (%) = 212 (25), 181 (8), 138 (100), 123 (44), 106 (45), 91 (28), 74 (22), 67 (14), 55 (25), 41 (42).

Representative Procedure for the Alkylation of Esters 24 and 38a involving Propargyl Bromides 25a and 25b: To a solution of lithium diisopropylamide [obtained from diisopropylamine (1.5 equiv.) and *n*-butyllithium (2.5 M in *n*-hexane, 1.5 equiv.)] in tetrahydrofuran (0.5 M) was added dropwise at –40 °C a solution of the ester (1.0 equiv.) in tetrahydrofuran (0.3 M). After stirring for 1 h at –40 °C, propargylic bromide **25a** or **25b** (3 equiv.) was added dropwise. After 30 min the reaction mixture was warmed to 20 °C and further stirred overnight. After addition of a saturated solution of ammonium chloride the aqueous phase was extracted with *tert*-butyl methyl ether and the organic phase dried (magnesium sulfate). After concentration in vacuo the residue was purified by column chromatography with pentane/ethyl acetate (98:2) to afford the alkylated esters. From **24** (0.14 g, 0.57 mmol) was obtained 0.19 g of **26** (74% yield) and from **38a** (0.29 g, 1.2 mmol) 0.37 g of **40** (68% yield).

26: R_f = 0.55 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = –15.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, *J* = 2.8 Hz, 1 H), 3.70 (s, 3 H), 3.43 (s, 3 H), 3.39 (s, 3 H), 2.97 (ddd, *J* = 9.5, 4.4, 3.5 Hz, 1 H), 2.51 (dd, *J* = 16.7, 9.8 Hz, 1 H), 2.22 (dd, *J* = 16.7, 4.4 Hz, 1 H), 1.79 (m, 2 H), 1.56 (m, 1 H), 1.47 (m, 1 H), 1.43 (m, 1 H), 1.41 (s, 6 H), 1.33 (m, 1 H), 1.15 (m, 2 H), 1.08 (qd, *J* = 12.3, 3.5 Hz, 1 H), 1.01 (d, *J* = 6.3 Hz, 3 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 0.64 (d, *J* = 7.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9 (C=O), 107.8 (CH), 85.9 (C), 81.2 (C), 66.2 (C), 56.7 (OCH_3), 56.2 (OCH_3), 51.7 (OCH_3), 47.3 (CH), 46.0 (CH), 45.8 (CH), 34.9 (CH), 33.2 (2 × CH_3), 27.0 (CH_2), 25.5 (CH_2), 24.4 (CH_2), 15.9 (CH_3), 14.9 (CH_3), 7.0 (CH_3), 6.2 (CH_2) ppm. IR: $\tilde{\nu}$ = 2952 (vs), 2876 (s), 2831 (m), 2240 (vw), 1739 (vs), 1542 (vw), 1451 (m), 1375 (m), 1313 (m), 1244 (s), 1165 (vs), 1078 (s), 1037 (vs), 954 (m), 926 (m), 740 (s) cm^{-1}. MS: *m*/*z* (%) = 425 (14), 335 (5), 219 (4), 191 (8), 159 (17), 143 (6), 117 (17), 87 (10), 75 (100), 47 (19). $C_{25}H_{46}O_5Si$ (454.72): calcd. C 66.03, H 10.20; found C 65.38, H 10.11.

40: R_f = 0.42 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = –11.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.84 (d, *J* = 6.6 Hz, 1 H), 3.57 (s, 3 H), 3.19 (s, 3 H), 3.18 (s, 3 H), 2.78 (dt, *J* = 9.1, 3.8 Hz, 1 H), 2.40 (dd, *J* = 16.7, 10.1 Hz, 1 H), 2.10 (dd, *J* = 16.7, 4.7 Hz, 1 H), 1.63 (m, 2 H), 1.45 (m, 2 H), 1.37 (m, 1 H), 1.26 (s, 6 H), 1.19 (m, 1 H), 0.90 (m, 2 H), 0.83 (d, *J* = 6.6 Hz, 3 H), 0.74 (q, *J* = 12.0 Hz, 1 H), 0.72 (s, 9 H), 0.00 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7 (C=O), 108.4 (CH), 86.1 (C), 81.2 (C), 66.3 (C-O), 54.1 (OCH_3), 53.7 (OCH_3), 51.7 (OCH_3), 46.4 (CH), 45.4 (CH), 40.4 (CH), 35.2 (CH_2), 34.3 (CH), 33.1 (2 × CH_3), 28.9 (CH_2), 27.5 (CH_2), 25.7 (3 × CH_3), 19.8 (CH_3), 17.9 (SiC), 15.3 (CH_2), –3.1 (2 × $SiCH_3$) ppm. IR: $\tilde{\nu}$ = 2981 (m), 2952 (vs), 2929 (vs), 2856 (s), 1740 (vs), 1462 (m), 1436 (m), 1376 (m), 1360 (m), 1248 (s), 1161 (vs), 1135 (m), 1038 (vs), 960 (w), 906 (w), 837 (s), 777 (s) cm^{-1}.

MS: *m*/*z* (%) = 398 (9), 365 (5), 307 (5), 199 (6), 159 (13), 131 (4), 107 (9), 89 (15), 75 (100), 47 (14).

Representative Procedure for the Methylation of Esters 24, 38a, and 38b: To a solution of lithium diisopropylamide [obtained from diisopropylamine (2.0 equiv.) and *n*-butyllithium (2.5 M in *n*-hexane, 2.0 equiv.)] in tetrahydrofuran (1.5 M) was added dropwise at –78 °C a solution of the ester (1.0 equiv.) in tetrahydrofuran (0.3 M). After stirring for 1 h at –78 °C, iodomethane (5 equiv.) was added dropwise. After stirring for 2 h water was added to the reaction mixture. After extraction with *tert*-butyl methyl ether, the organic phase was dried (magnesium sulfate) and concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (93:7) to afford the methylated ester(s) as an oil. Further purification was performed by HPLC with cyclohexane/*tert*-butyl methyl ether (9:1). From ester **24** (0.5 g, 2.0 mmol) was obtained ester **27** (ratio 92:8; 0.47 g, 89% yield); from ester **38a** (0.32 g, 1.3 mmol) ester **39** (ratio 94:6; 0.29 g, 87% yield); in the case of **38b** (0.75 g, 3.1 mmol) a 1:1 mixture of epimeric esters **45** (0.8 g) was obtained, which was not separated but directly reduced with lithium aluminum hydride.

27: R_f = 0.44 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = –44.3 (*c* = 1.86, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, *J* = 1.9 Hz, 1 H), 3.66 (s, 3 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.83 (dq, *J* = 7.3, 3.8 Hz, 1 H), 1.78 (m, 2 H), 1.61 (m, 1 H), 1.35 (m, 2 H), 1.29 (m, 1 H), 1.19 (m, 1 H), 1.14 (m, 2 H), 0.99 (d, *J* = 7.3 Hz, 3 H), 0.94 (d, *J* = 5.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1 (C=O), 107.9 (CH), 56.8 (OCH_3), 56.1 (OCH_3), 51.6 (OCH_3), 47.2 (CH), 45.5 (CH), 40.0 (CH), 34.6 (CH), 26.6 (CH_2), 25.6 (CH_2), 24.5 (CH_2), 15.0 (CH_3), 9.0 (CH_3) ppm. IR: $\tilde{\nu}$ = 2972 (m), 2929 (s), 2831 (m), 1736 (vs), 1449 (m), 1372 (m), 1305 (m), 1199 (s), 1140 (s), 1072 (s), 1047 (m), 962 (m), 852 (w), 768 (vw) cm^{-1}. MS: *m*/*z* (%) = 227 [M^+], 195 (2), 138 (3), 123 (1), 107 (7), 95 (3), 88 (3), 75 (100), 59 (7), 55 (7), 47 (9).

39: R_f = 0.41 (*i*-octane/EtOAc, 4:6). $[\alpha]_D$ = –5.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (d, *J* = 6.9 Hz, 1 H), 3.66 (s, 3 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 2.77 (qd, *J* = 7.1, 3.6 Hz, 1 H), 1.74 (m, 2 H), 1.63 (m, 1 H), 1.55 (tt, *J* = 11.5, 3.6 Hz, 1 H), 1.42 (m, 1 H), 1.20 (m, 1 H), 1.04 (m, 2 H), 0.99 (d, *J* = 7.3 Hz, 3 H), 0.89 (q, *J* = 12.5 Hz, 1 H), 0.88 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9 (C=O), 108.5 (CH), 53.8 (OCH_3), 53.7 (OCH_3), 51.6 (OCH_3), 45.1 (CH), 40.3 (CH), 40.1 (CH), 35.1 (CH_2), 33.9 (CH), 28.3 (CH_2), 27.6 (CH_2), 19.5 (CH_3), 9.3 (CH_3) ppm. IR: $\tilde{\nu}$ = 2949 (vs), 2916 (s), 2830 (m), 1737 (vs), 1456 (m), 1383 (m), 1244 (m), 1201 (s), 1149 (s), 1132 (s), 1092 (s), 1056 (s), 959 (m) cm^{-1}. MS: *m*/*z* (%) = 195 (4), 163 (2), 135 (4), 107 (16), 81 (5), 75 (100), 47 (15), 41 (16).

Representative Procedure for the Reduction with Lithium Aluminum Hydride of Esters 26 and 40: To a solution of the ester (1.0 equiv.) in diethyl ether (0.3 M) was added at 0 °C lithium aluminum hydride (1.5 equiv.). The reaction mixture was stirred for 1 h at room temperature, cooled to 0 °C, and treated successively with water, a sodium hydroxide solution (15%), and again with water. The reaction mixture was further stirred for 1 h at room temperature. After filtration of the white precipitate over Celite, the filtrate was concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (8:2). From ester **26** (0.36 g, 0.8 mmol) was obtained 0.32 g of **28** (94% yield); from ester **40** (0.14 g, 0.31 mmol) 0.12 g of **43** (94% yield).

28: R_f = 0.42 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = +1.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (d, *J* = 2.5 Hz, 1 H), 3.82 (ddd, *J* = 10.7, 6.0, 4.4 Hz, 1 H), 3.56 (dt, *J* = 10.7, 6.6 Hz, 1 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.25 (dd, *J* = 16.5, 4.4 Hz, 1 H), 2.17 (m, 1 H), 2.00 (dd, *J* = 16.5, 9.8 Hz, 1 H), 1.80 (m, 2 H), 1.68 (dd, *J* = 6.6, 4.4 Hz, 1 H), 1.53 (m, 1 H), 1.44 (s, 6 H), 1.42 (m, 1 H), 1.32 (m, 1 H), 1.29 (m, 1 H), 1.15 (m, 2 H), 0.99 (m, 1 H), 0.96 (m, 12 H), 0.65 (d, *J* = 7.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 107.9 (CH), 86.9 (C), 81.8 (C), 66.3 (C), 66.0 (CH_2OH), 56.8 (OCH_3), 56.1 (OCH_3), 47.4 (CH), 44.4 (CH), 40.2 (CH), 34.7 (CH), 33.2 ($2\times CH_3$), 25.8 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 15.9 (CH_3), 15.7 (CH_3), 7.0 (CH_3), 6.1 (CH_2) ppm. IR: $\tilde{\nu}$ = 3432 (m), 2931 (m), 2874 (m), 1458 (m), 1375 (m), 1244 (m), 1157 (s), 1120 (m), 1070 (s), 1032 (vs), 961 (m), 767 (m), 741 (vs), 725 (vs) cm^{-1}. MS: *m*/*z* (%) = 379 (1), 365 (8), 333 (4), 305 (1), 263 (1), 243 (10), 213 (8), 173 (9), 145 (8), 117 (11), 103 (12), 75 (100), 47 (14).

43: R_f = 0.24 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = –18.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.96 (d, *J* = 6.6 Hz, 1 H), 3.83 (dd, *J* = 10.8, 6.6 Hz, 1 H), 3.57 (dd, *J* = 10.8, 6.6 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.23 (dd, *J* = 16.4, 4.4 Hz, 1 H), 2.11 (m, 1 H), 2.01 (dd, *J* = 16.4, 9.5 Hz, 1 H), 1.74 (m, 2 H), 1.59 (m, 3 H), 1.41 (s, 6 H), 1.29 (m, 1 H), 1.24 (m, 1 H), 1.02 (m, 2 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 0.84 (s, 9 H), 0.78 (q, *J* = 12.3 Hz, 1 H), 0.13 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.6 (CH), 87.0 (C), 81.9 (C), 66.4 (CO), 65.6 (CH_2OH), 54.1 (OCH_3), 53.5 (OCH_3), 44.0 (CH), 40.5 (CH), 40.4 (CH), 35.4 (CH_2), 33.9 (CH), 33.1 ($2\times CH_3$), 27.8 (CH_2), 27.2 (CH_2), 25.7 ($3\times CH_3$), 19.8 (CH_3), 17.9 (SiC), 15.9 (CH_2), –2.9 ($2\times SiCH_3$) ppm. IR: $\tilde{\nu}$ = 3430 (br. s, m), 2952 (vs), 2929 (vs), 2856 (s), 2235 (vw), 1472 (m), 1462 (m), 1377 (m), 1360 (m), 1248 (s), 1160 (vs), 1040 (vs), 957 (w), 905 (w), 837 (s), 776 (s), 681 (w) cm^{-1}. MS: *m*/*z* (%) = 337 (3), 305 (4), 279 (1), 231 (1), 213 (3), 203 (2), 171 (4), 145 (5), 133 (5), 107 (7), 91 (8), 75 (100), 47 (15), 41 (13).

The Three-Step Sequence to Intermediates 31 and 44

Step 1: To a solution of alcohol **28** (1.0 equiv., 0.14 g, 0.32 mmol) in dichloromethane (0.1 M) was added triethylamine (4 equiv.), tosyl chloride (3.0 equiv.), and a catalytic amount of 4-dimethylaminopyridine at 0 °C. After stirring for 4 h at room temperature water was added to the reaction mixture. After extraction with dichloromethane, the organic phase was dried (magnesium sulfate) and concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (92:8), yielding 0.31 g (90% yield) of tosylate **29** as an oil. R_f = 0.48 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = +13.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.30 (d, *J* = 2.5 Hz, 1 H), 4.16 (dd, *J* = 9.5, 5.2 Hz, 1 H), 3.93 (t, *J* = 9.5 Hz, 1 H), 3.42 (s, 3 H), 3.39 (s, 3 H), 2.44 (s, 3 H), 2.31 (m, 1 H), 2.21 (dd, *J* = 17.0, 4.7 Hz, 1 H), 1.87 (dd, *J* = 17.0, 9.8 Hz, 1 H), 1.77 (m, 1 H), 1.72 (m, 1 H), 1.40 (m, 1 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.28 (m, 3 H), 1.07 (m, 2 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 0.86 (m, 1 H), 0.60 (d, *J* = 7.9 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.8 (C), 133.1 (C), 129 ($2\times$C=), 128.0 ($2\times$C=), 107.8 (CH), 87.3 (C), 80.1 (C), 71.3 (CH_2OH), 66.2 (C), 56.7 (OCH_3), 56.1 (OCH_3), 47.3 (CH), 42.7 (CH), 37.2 (CH), 34.5 (CH), 33.1 ($2\times CH_3$), 25.6 (CH_2), 25.1 (CH_2), 24.4 (CH_2), 21.6 (CH_3), 15.5 (CH_3), 15.1 (CH_2), 7.0 (CH_3), 6.1 (CH_2) ppm. IR: $\tilde{\nu}$ = 2932 (m), 1715 (vw), 1598 (vw), 1478 (w), 1365 (s), 1244 (w), 1188 (s), 1176 (vs), 1158 (s), 1069 (s), 1034 (s), 969 (s), 834 (s), 814 (s), 742 (s), 666 (vs) cm^{-1}. MS: *m*/*z* (%) = 401 (1), 335 (1), 257 (26), 213 (16), 173 (6), 165 (7), 105 (6), 91 (21), 75 (100), 47 (16). (b)

Step 2: To a solution of tosylate **29** (1.0 equiv.) in tetrahydrofuran (0.03 M) was added lithium aluminum hydride (4.0 equiv.). After stirring overnight a saturated solution of sodium sulfate was added, the mixture was further stirred for 30 min at room temperature, and the suspension was filtered through a short pad of Celite. After

concentration of the filtrate in vacuo the residue was purified by column chromatography with pentane/ethyl acetate (87:3) to afford 0.10 g of **30** in 89% yield. R_f = 0.59 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = +2.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (d, *J* = 2.5 Hz, 1 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.19 (dd, *J* = 16.4, 3.8 Hz, 1 H), 2.09 (m, 1 H), 1.80 (dd, *J* = 16.4, 10.1 Hz, 1 H), 1.79 (m, 2 H), 1.64 (m, 1 H), 1.44 (s, 6 H), 1.39 (m, 1 H), 1.28 (m, 1 H), 1.14 (m, 2 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.00 (m, 1 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.95 (d, *J* = 6.0 Hz, 3 H), 0.88 (qd, *J* = 12.3, 3.2 Hz, 1 H), 0.66 (d, *J* = 7.9 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.1 (CH), 86.0 (C≡), 82.7 (C≡), 66.3 (C), 56.8 (OCH_3), 56.0 (OCH_3), 48.9 (CH), 47.6 (CH), 35.1 (CH), 33.3 (2×CH_3), 32.4 (CH_2), 26.0 (CH_2), 25.1 (CH_2), 24.5 (CH_3), 19.9 (CH_2), 18.9 (CH_3), 15.7 (CH_3), 7.0 (CH_3), 6.3 (CH_2) ppm. IR: $\tilde{\nu}$ = 2931 (m), 2874 (m), 1458 (m), 1375 (m), 1245 (m), 1157 (vs), 1114 (m), 1073 (s), 1034 (vs), 961 (m), 904 (w), 768 (m), 741 (vs), 725 (vs) cm^{-1}. MS: *m*/*z* (%) = 363 (2), 349 (2), 291 (1), 249 (1), 233 (3), 205 (6), 175 (18), 147 (7), 117 (23), 105 (10), 75 (100), 47 (13).

Step 3: To a solution of alkyne **30** (1.0 equiv.) in ethyl acetate (0.1 M) was added molecular sieves (3.0 equiv.) and platinum oxide (5 mol-%). The flask was flushed with hydrogen and the mixture stirred overnight under an atmosphere of hydrogen. After completion of the reaction (TLC development with anisaldehyde) the reaction mixture was filtered through Celite. After concentration of the filtrate in vacuo the residue was purified by HPLC with isooctane/ethyl acetate (96:4) to afford 0.1 g of **31** (98% yield). In the same way, alcohol **43** (0.06 g, 0.14 mmol) was converted into 0.045 g of compound **44** in 80% overall yield.

31: R_f = 0.62 (*i*-octane/EtOAc, 7:3). $[\alpha]_D$ = +6.0 (*c* = 1.0, $CHCl_3$). ^{1}HNMR (500 MHz, $CDCl_3$): δ = 4.34 (d, *J* = 2.8 Hz, 1 H), 3.45 (s, 3 H), 3.40 (s, 3 H), 1.80 (m, 3 H), 1.62 (m, 1 H), 1.44 (m, 2 H), 1.40 (m, 1 H), 1.35 (m, 1 H), 1.28 (m, 2 H), 1.18 (s, 6 H), 1.15 (m, 1 H), 1.14 (m, 2 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.89 (m, 3 H), 0.66 (d, *J* = 7.9 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.2 (CH), 73.2 (C), 56.8 (OCH_3), 56.0 (OCH_3), 47.6 (CH), 45.4 (CH_2), 34.9 (CH), 32.2 (CH), 30.4 (CH_2), 30.0 (CH_3), 29.9 (CH_3), 26.2 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 23.0 (CH_3), 18.7 (CH_3), 15.7 (CH_3), 7.1 (CH_3), 6.8 (CH_2) ppm. IR: $\tilde{\nu}$ = 2931 (s), 2847 (m), 1459 (m), 1377 (m), 1364 (m), 1233 (m), 1212 (m), 1159 (m), 1123 (m), 1073 (vs), 1042 (vs), 1016 (s), 961 (s), 741 (vs), 721 (vs) cm^{-1}. MS: *m*/*z* (%) = 382 (1), 353 (2), 219 (2), 173 (17), 163 (7), 135 (5), 103 (15), 75 (100), 69 (11), 47 (11).

44: R_f = 0.56 (*i*-octane/EtOAc, 9:1). $[\alpha]_D$ = –21.9 (*c* = 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 7.0 Hz, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 1.76 (m, 1 H), 1.72 (m, 3 H), 1.57 (m, 1 H), 1.44 (m, 2 H), 1.32 (m, 1 H), 1.25 (m, 2 H), 1.19 (m, 1 H), 1.17 (s, 6 H), 0.99 (m, 2 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.89 (m, 1 H), 0.85 (m, 12 H), 0.70 (q, *J* = 12.2 Hz, 1 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.9 (CH), 73.6 (COH), 53.9 (OCH_3), 53.6 (OCH_3), 49.8 (CH), 45.5 (CH_2), 40.7 (CH), 35.8 (CH_2), 34.1 (CH_2), 32.8 (CH), 30.9 (CH_2), 30.0 (CH_3), 29.9 (CH_3), 28.2 (CH_2), 27.2 (CH_2), 25.9 (3×CH_3), 23.0 (CH_2), 20.0 (CH_3), 18.5 (CH_3), 18.2 (CSi), –2.0 (2×$SiCH_3$) ppm. IR: $\tilde{\nu}$ = 2951 (s), 2926 (s), 2854 (m), 1461 (m), 1380 (m), 1363 (m), 1251 (s), 1211 (m), 1169 (m), 1130 (s), 1053 (vs), 1005 (m), 955 (m), 864 (w), 833 (vs), 770 (vs), 689 (m) cm^{-1}. MS: *m*/*z* (%) = 251 (1), 219 (3), 173 (15), 163 (8), 135 (2), 107 (10), 95 (11), 75 (100), 55 (8), 41 (7).

14: R_f = 0.46 (*i*-octane/EtOAc, 5:5). M.p. 93 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 4.51 (d, *J* = 4.7 Hz, 1 H), 3.89 (m, 4 H), 3.83 (m, 2 H), 2.44 (s, 3 H), 2.17 (m, 1 H), 1.72 (m, 2 H), 1.46 (m, 1 H), 1.31 (m, 1 H), 1.20 (m, 1 H), 1.10 (m, 1 H), 1.02 (m, 2 H), 0.81 (q, *J* = 12.3 Hz, 1 H), 0.79 (d, *J* = 6.3 Hz, 3 H), 0.72 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.6 (C=), 133.2 (C=), 129.9 (2×=CH), 127.9 (2×=CH), 107.3 (CHO_2), 74.4 (CH_2O), 65.0 (2×CH_2O), 43.3 (CH), 41.4 (CH), 35.0 (CH_2), 33.7 (CH), 32.6 (CH), 26.7 (CH_2), 25.7 (CH_2), 21.7 (CH_3), 19.4 (CH_3), 9.9 (CH_3) ppm. IR: $\tilde{\nu}$ = 2918 (s), 2876 (s), 1598 (w), 1458 (w), 1360 (vs), 1189 (vs), 1178 (vs), 1097 (m), 958 (vs), 845 (vs), 816 (vs) cm^{-1}. MS: *m*/*z* (%) = 336 (3), 21 (3), 155 (5), 149 (4), 136 (3), 107 (5), 91 (21), 81 (10), 73 (100), 45 (15), 41 (6).

Representative Procedure for the Reduction with Lithium Aluminum Hydride of Esters 27 and 39 and the mixture of 45: To a solution of the ester (1.0 equiv.) in diethyl ether (0.3 M) was added at 0 °C lithium aluminum hydride (1.5 equiv.). The resulting reaction mixture was stirred for 1 h at room temperature, cooled (0 °C), and treated successively with water, aqueous solution of sodium hydroxide (15%), and water again. After further stirring for 1 h at room temperature the white precipitate was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (8:2). From ester **27** (0.74 g, 2.86 mmol) was obtained 0.625 g of alcohol **33** (95% yield); from ester **39** (100 mg, 0.39 mmol) 85 mg of **41** (85% yield). In the case of **45** (0.80 g) a 1:1 mixture of alcohols **46a** and **15** was obtained (584 mg, 82% yield).

33: R_f = 0.45 (*i*-octane/EtOAc, 3:7). $[\alpha]_D$ = –5.0 (*c* = 1.87, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.34 (d, *J* = 2.5 Hz, 1 H), 3.49 (m, 2 H), 3.44 (s, 3 H), 3.39 (s, 3 H), 2.04 (m, 1 H), 1.80 (m, 2 H), 1.45 (m, 1 H), 1.37 (m, 1 H), 1.32 (s, 1 H), 1.30 (m, 1 H), 1.22 (m, 1 H), 1.14 (m, 2 H), 1.00 (qd, *J* = 12.3, 2.5 Hz, 1 H), 0.93 (d, *J* = 6.0 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.1 (CH), 76.3 (CH_2OH), 56.8 (OCH_3), 56.0 (OCH_3), 47.4 (CH), 43.9 (CH), 35.3 (CH), 34.6 (CH), 25.7 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 15.5 (CH_3), 10.2 (CH_3) ppm. IR: $\tilde{\nu}$ = 3409 (br. s), 2929 (vs), 2873 (s), 1448 (m), 1375 (m), 1305 (vw), 1170 (m), 1122 (m), 1072 (vs), 1044 (s), 958 (m), 913 (w), 851 (w) cm^{-1}. MS: *m*/*z* (%) = 149 (2), 121 (2), 109 (3), 95 (3), 81 (6), 75 (100), 67 (8), 47 (16), 41 (14). $C_{14}H_{26}O_4$ (258.35): calcd. C 67.79, H 11.38; found C 67.80, H 12.11.

41: R_f = 0.33 (*i*-octane/EtOAc, 5:5). $[\alpha]_D$ = –20.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.03 (d, *J* = 6.7 Hz, 1 H), 3.56 (m, 2 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.06 (sxd, *J* = 7.2, 2.9 Hz, 1 H), 1.78 (m, 2 H), 1.66 (m, 1 H), 1.58 (m, 1 H), 1.40 (t, *J* = 4.6 Hz, 1 H), 1.29 (m, 1 H), 1.22 (tt, *J* = 11.6, 3.0 Hz, 1 H), 1.06 (m, 2 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.83 (q, *J* = 12.1 Hz, 1 H), 0.81 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 67.0 (CH_2OH), 54.0 (OCH_3), 53.6 (OCH_3), 43.6 (CH), 40.3 (CH), 35.6 (CH), 35.4 (CH_2), 33.8 (CH), 27.9 (CH_2), 26.3 (CH_2), 19.6 (CH_3), 10.2 (CH_3) ppm. IR: $\tilde{\nu}$ = 3421 (br. s, m), 2950 (vs), 2917 (vs), 2874 (vs), 1455 (m), 1380 (m), 1193 (m), 1129 (vs), 1096 (vs), 1059 (vs), 957 (s), 984 (m), 957 (m), 756 (m) cm^{-1}. MS: *m*/*z* (%) = 107 (5), 93 (5), 81 (5), 75 (100), 55 (15), 41 (16).

46a: R_f = 0.31 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = +10.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (d, *J* = 6.9 Hz, 1 H), 3.64 (dt, *J* = 10.7, 4.3 Hz, 1 H), 3.46 (dt, *J* = 10.7, 5.6 Hz, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 1.95 (m, 1 H), 1.64 (m, 1 H), 1.58 (m, 2 H), 1.47 (m, 3 H), 1.31 (m, 1 H), 1.16 (m, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.88 (m, 1 H), 0.83 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 66.1 (CH_2OH), 54.0 (OCH_3), 53.6 (OCH_3), 41.5 (CH), 41.0 (CH), 37.5 (CH), 33.1 (CH_2), 29.2 (CH), 24.9 (CH_2), 21.7 (CH_2), 15.3 (CH_3), 12.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3418 (m), 2928 (vs), 2830 (m), 1458 (m), 1442 (m), 1382 (m), 1189 (m), 1126 (s), 1088 (s), 1054 (vs), 985 (m), 962 (m), 756 (m)

cm^{-1}. MS: *m*/*z* (%) = 149 (3), 107 (4), 93 (4), 75 (100), 55 (9), 47 (14).

15: R_f = 0.23 (*i*-octane/EtOAc: 1:1). M.p. 66 °C. $[\alpha]_D$ = +7.4 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 6.9 Hz, 1 H), 3.70 (dt, *J* = 10.2, 4.2 Hz, 1 H), 3.52 (dt, *J* = 10.2, 5.7 Hz, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 1.98 (m, 1 H), 1.67 (m, 1 H), 1.61 (m, 1 H), 1.56 (m, 1 H), 1.50 (m, 1 H), 1.45 (m, 1 H), 1.38 (m, 1 H), 1.27 (m, 1 H), 1.18 (qd, *J* = 12.3, 3.5 Hz, 1 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.89 (qd, *J* = 12.6, 3.1 Hz, 1 H), 0.80 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 66.4 (CH_2OH), 54.1 (OCH_3), 53.6 (OCH_3), 41.2 (CH), 40.7 (CH), 38.5 (CH), 33.0 (CH_2), 28.3 (CH), 25.4 (CH_2), 21.6 (CH_2), 14.9 (CH_3), 11.8 (CH_3) ppm. IR: $\tilde{\nu}$ = 3418 (m), 2925 (vs), 2831 (m), 1465 (m), 1442 (m), 1389 (m), 1188 (m), 1129 (s), 1086 (s), 1054 (vs), 988 (m), 853 (m) cm^{-1}. MS: *m*/*z* (%) = 149 (3), 107 (5), 93 (6), 75 (100), 67 (9), 47 (19).

The Three-Step Synthesis of Intermediates 37, 42, 47a, and 47b

Step 1: To a solution of oxalyl chloride (1.1 equiv.) in dichloromethane (0.3 M) was added at –78 °C dropwise a solution of dimethyl sulfoxide (2.2 equiv.) in dichloromethane (3 M), followed by a solution of alcohol **33** (1 equiv., 200 mg, 0.686 mmol) in dichloromethane (0.5 M). After stirring for 15 min at –78 °C triethylamine (5 equiv.) was added, and the reaction mixture was slowly brought to room temperature. After addition of water and *tert*-butyl methyl ether the mixture was partly concentrated in vacuo. The organic phase obtained after the addition of *tert*-butyl methyl ether was washed with water, dried (magnesium sulfate), and concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (9:1) to afford pure aldehyde **34**. R_f = 0.60 (*i*-octane/EtOAc, 3:7). $[\alpha]_D$ = –64.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.65 (s, 1 H), 4.33 (d, *J* = 2.5 Hz, 1 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.66 (qd, *J* = 6.9, 3.2 Hz, 1 H), 1.81 (m, 1 H), 1.76 (m, 1 H), 1.71 (m, 1 H), 1.41 (m, 2 H), 1.22 (m, 2 H), 1.15 (m, 1 H), 1.10 (m, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.96 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.2 (CHO), 107.9 (CH), 56.7 (OCH_3), 56.2 (OCH_3), 47.4 (CH), 47.3 (CH), 43.2 (CH), 34.4 (CH), 26.9 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 15.7 (CH_3), 6.5 (CH_3) ppm. IR: $\tilde{\nu}$ = 2979 (vs), 2936 (vs), 2872 (s), 2722 (vw), 1721 (vs), 1618 (vw), 1451 (m), 1403 (m), 1378 (m), 1327 (w), 1301 (w), 1256 (w), 1223 (m), 1171 (m), 1127 (s), 1070 (vs), 989 (m), 950 (s), 909 (w), 654 (w) cm^{-1}. MS: *m*/*z* (%) = 107 (6), 95 (6), 81 (4), 75 (100), 67 (6), 55 (9), 41 (10).

Step 2: To a solution of phosphonium bromide **35** (2.0 equiv.) in tetrahydrofuran (0.25 M) was added at –20 °C dropwise a solution of methyllithium (4 equiv.) in diethyl ether (1.6 M). The reaction mixture was further stirred for 1 h at –20 °C and for 3 h at room temperature. The red-colored solution of the ylide was treated at –40 °C with a solution of aldehyde **34** (0.2 M, 1 equiv.). The reaction mixture was slowly brought to room temperature and further stirred for 1 h. After addition of water and extraction with *tert*-butyl methyl ether, the organic phase was dried (magnesium sulfate) and concentrated in vacuo. The residue was treated with silica gel (by successive addition of dichloromethane and concentration), and the obtained solid phase was purified by column chromatography with pentane/ethyl acetate (93:7). Pure alkene **36** (218 mg, 84% yield) was obtained by further HPLC with isooctane/ethyl acetate (8:2). R_f = 0.45 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = –23.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.55 (dd, *J* = 15.5, 6.0 Hz, 1 H), 5.42 (dt, *J* = 15.5, 7.3 Hz, 1 H), 4.33 (d, *J* = 2.2 Hz, 1 H), 3.44 (s, 3 H), 3.39 (s, 3 H), 2.58 (m, 1 H), 2.17 (d, *J* = 7.3 Hz, 2 H), 1.78 (m, 2 H), 1.52 (m, 1 H), 1.36 (m, 1 H), 1.30 (m, 1 H), 1.19 (s, 6 H), 1.13 (m, 2 H), 1.06 (m, 1 H), 0.97 (m, 1 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.3 (=CH), 123.3 (=CH), 108.1 (CH), 70.4 (C), 56.8 (OCH_3), 56.0 (OCH_3), 48.7 (CH), 47.4 (CH), 47.1 (CH_2), 35.6 (CH), 34.9 (CH), 29.0 ($2\times CH_2$), 25.9 (CH_2), 25.4 (CH_2), 24.6 (CH_2), 14.6 (CH_3), 11.1 (CH_3) ppm. IR: $\tilde{\nu}$ = 3416 (br. w), 2967 (m), 2929 (m), 1448 (m), 1374 (m), 1202 (m), 1155 (m), 1118 (s), 1068 (vs), 961 (s), 905 (m), 753 (vs), 666 (w) cm^{-1}. MS: *m*/*z* (%) = 208 (3), 161 (3), 147 (1), 139 (3), 107 (10), 93 (6), 75 (100), 59 (41), 41 (13).

Step 3: To a solution of alkene **36** (1.0 equiv.) in ethyl acetate (0.1 M) was added molecular sieves (3.0 equiv.) and rhodium/C. The flask was flushed with hydrogen, and the mixture was stirred overnight under an atmosphere of hydrogen. The mixture was filtered through Celite and the filtrate concentrated in vacuo to afford 217 mg of compound **37** in quantitative yield. In the same way starting from alcohol **41** (95 mg, 0.412 mmol) was obtained intermediate **42** (78 mg, 63% overall yield), from alcohol **46a** (67 mg, 0.29 mmol) intermediate **47a** (55 mg, 63% overall yield), and from alcohol **15** (70 mg, 0.304 mmol) intermediate **47b** (60 mg, 66% overall yield).

37: R_f = 0.44 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = –9.7 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.33 (d, *J* = 2.5 Hz, 1 H), 3.44 (s, 3 H), 3.39 (s, 3 H), 1.79 (m, 3 H), 1.51 (m, 1 H), 1.44 (m, 2 H), 1.32 (m, 4 H), 1.21 (s, 6 H), 1.20 (m, 1 H), 1.13 (m, 2 H), 0.99 (m, 1 H), 0.95 (m, 1 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.72 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.1 (CH), 71.0 (C), 56.8 (OCH_3), 56.0 (OCH_3), 47.5 (CH), 47.2 (CH), 44.3 (CH_2), 36.3 (CH_2), 34.9 (CH), 32.1 (CH), 29.3 ($2\times CH_2$), 26.0 (CH_2), 24.6 (CH_2), 24.5 (CH_2), 22.6 (CH_2), 15.5 (CH_3), 13.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3421 (br. w), 2961 (m), 2931 (m), 1462 (m), 1448 (m), 1378 (m), 1201 (m), 1164 (m), 1119 (m), 1069 (s), 959 (m), 945 (m), 752 (vs), 666 (m) cm^{-1}. MS: *m*/*z* (%) = 221 (2), 203 (2), 163 (1), 149 (2), 149 (2), 109 (4), 95 (7), 75 (100), 59 (20), 41 (10).

42: R_f = 0.40 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = –13.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 6.6 Hz, 1 H), 3.33 (s, 6 H), 1.74 (m, 3 H), 1.61 (m, 1 H), 1.58 (m, 1 H), 1.45 (t, *J* = 7.3 Hz, 2 H), 1.35 (m, 2 H), 1.23 (m, 3 H), 1.21 (s, 6 H), 0.94 (m, 1 H), 0.85 (d, *J* = 6.3 Hz, 3 H), 0.73 (d, *J* = 6.9 Hz, 3 H), 0.72 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 71.1 (C), 53.6 ($2\times OCH_3$), 47.1 (CH), 44.3 (CH_2), 40.4 (CH), 36.0 (CH_2), 35.5 (CH_2), 34.1 (CH), 32.4 (CH), 29.3 ($2\times CH_3$), 28.0 (CH_2), 26.1 (CH_2), 22.6 (CH_2), 19.7 (CH_3), 13.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3425 (w), 2929 (s), 2868 (m), 1455 (m), 1378 (m), 1362 (m), 1192 (m), 1152 (m), 1132 (s), 1096 (s), 1053 (vs), 981 (m), 955 (s), 936 (m), 903 (m), 765 (vw) cm^{-1}. MS: *m*/*z* (%) = 221 (1), 203 (1), 165 (4), 149 (1), 137 (2), 123 (2), 107 (4), 95 (4), 81 (3), 75 (100), 59 (14), 45 (4).

47a: R_f = 0.45 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = +25.3 (*c* = 1.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.98 (d, *J* = 6.9 Hz, 1 H), 3.33 (s, 3 H), 3.31 (s, 3 H), 1.98 (m, 1 H), 1.65 (m, 1 H), 1.61 (m, 2 H), 1.51 (m, 2 H), 1.45 (m, 4 H), 1.29 (m, 2 H), 1.25 (s, 6 H), 1.17 (m, 2 H), 1.09 (m, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.87 (q, *J* = 12.6 Hz, 1 H), 0.83 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 71.1 (C), 53.8 (OCH_3), 53.5 (OCH_3), 44.8 (CH), 44.4 (CH_2), 40.8 (CH), 34.5 (CH), 34.1 (CH_2), 33.2 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 28.2 (CH), 25.3 (CH_2), 21.7 (CH_2), 21.1 (CH_2), 17.4 (CH_3), 12.2 (CH_3) ppm. IR: $\tilde{\nu}$ = 3438 (m), 2964 (vs), 2936 (vs), 1466 (m), 1445 (m), 1379 (m), 1189 (m), 1155 (m), 1130 (m), 1075 (m), 1054 (s), 953 (m), 757 (vs) cm^{-1}. MS: *m*/*z* (%) = 268 (9), 250 (16), 235 (3), 203 (3), 165 (100), 137 (22), 123 (10), 107 (35), 85 (38), 79 (25), 59 (48), 55 (50), 41 (59).

47b: R_f = 0.45 (*i*-octane/EtOAc, 1:1). $[\alpha]_D$ = –11.2 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.00 (d, *J* = 6.9 Hz, 1 H), 3.34

(s, 3 H), 3.33 (s, 3 H), 2.00 (m, 1 H), 1.70 (m, 1 H), 1.60 (m, 1 H), 1.55 (m, 1 H), 1.47 (m, 4 H), 1.42 (m, 2 H), 1.23 (m, 2 H), 1.21 (s, 6 H), 1.19 (m, 1 H), 1.05 (m, 2 H), 0.86 (d, J = 6.3 Hz, 3 H), 0.83 (q, J = 12.6 Hz, 1 H), 0.78 (d, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.8 (CH), 71.1 (C), 53.7 (OCH_3), 53.6 (OCH_3), 44.8 (CH), 44.4 (CH_2), 40.8 (CH), 34.9 (CH), 34.7 (CH_2), 33.2 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 28.7 (CH), 25.3 (CH_2), 21.8 (CH_2), 21.5 (CH_2), 16.8 (CH_3), 11.9 (CH_3) ppm. IR: $\tilde{\nu}$ = 3436 (w), 2963 (s), 2933 (s), 2906 (s), 2829 (w), 1465 (m), 1442 (m), 1376 (m), 1188 (m), 1147 (s), 1128 (vs), 1075 (s), 1052 (vs), 986 (m), 961 (m), 937 (m), 906 (m), 755 (vs), 665 (w) cm^{-1}. MS: m/z (%) = 243 (1), 213 (15), 199 (39), 181 (15), 171 (7), 153 (19), 141 (12), 125 (6), 103 (100), 91 (40), 75 (88), 59 (22), 45 (42), 41 (27).

Synthesis of Analogues 5a, 5b, 6a, 6b, 7a, and 7b

Step 1: To a solution of the acetal (1.0 equiv.) in dichloromethane (0.1 M) was added at 0 °C 2,4,6-collidine (4 equiv.) followed by triethylsilyl trifluoromethanesulfonate (3.0 equiv.). After stirring the reaction mixture for 1 h at 0 °C, water was added and after further stirring for 30 min at room temperature the mixture was extracted with dichloromethane. The organic phase was dried (magnesium sulfate) and concentrated in vacuo. The residue was purified by column chromatography with pentane/ethyl acetate (98:2) to afford the corresponding aldehyde.

Step 2: To a solution resulting from the treatment of phosphane oxide **32** (2.2 equiv.) with *n*-butyllithium (2.5 M in hexane, 2.15 equiv.) in tetrahydrofuran (0.1 M) was added at –78 °C a solution of the aldehyde (1.0 equiv.) in tetrahydrofuran (0.15 M). After stirring of the reaction mixture at –78 °C for 90 min, the mixture was very slowly brought to 0 °C. After addition of water and extraction with *tert*-butyl methyl ether the organic phase was dried (magnesium sulfate) and concentrated in vacuo. The residue containing the protected analogue was further separated from the excess amount of phosphane oxide by column chromatography with pentane/ethyl acetate (98.5:1.5).

Step 3: To the above-obtained silyl ether was added a solution of tetrabutylammonium fluoride (1 M solution, 10 equiv.) in tetrahydrofuran. After overnight stirring at room temperature the reaction mixture was directly brought on a column and eluted with dichloromethane/acetone (6:4). The product was further purified by HPLC with dichloromethane/acetone (75:25). From acetal **31** (11 mg, 0.03 mmol) was obtained 10 mg of analogue **5a** (71% yield), from acetal **37** (10 mg, 0.033 mmol) 10 mg of analogue **5b** (76%), from acetal **42** (13 mg, 0.04 mmol) 12 mg of analogue **6a** (76% yield), from acetal **44** (25 mg, 0.083 mmol) 10 mg of analogue **6b** (33% yield), from acetal **47a** (18 mg, 0.06 mmol) 9.5 mg of analogue **7a** (43% yield), and from acetal **47b** (15 mg, 0.05 mmol) 13 mg of analogue **7b** (70% yield).

5a: R_f = 0.69 (acetone). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.33 (dd, J = 15.2, 10.7 Hz, 1 H), 6.03 (d, J = 10.7 Hz, 1 H), 5.52 (dd, J = 15.2, 8.9 Hz, 1 H), 5.30 (s, 1 H), 4.99 (s, 1 H), 4.43 (dd, J = 5.4, 5.0 Hz, 1 H), 4.21 (m, 1 H), 2.57 (dd, J = 13.2, 3.8 Hz, 1 H), 2.26 (dd, J = 13.2, 7.6 Hz, 1 H), 1.96 (m, 2 H), 1.80 (m, 1 H), 1.74 (m, 1 H), 1.62 (m, 3 H), 1.59 (s, 1 H), 1.47 (m, 2 H), 1.38 (m, 1 H), 1.28 (m, 1 H), 1.21 (s, 6 H), 1.16 (m, 2 H), 1.11 (m, 2 H), 0.92 (m, 3 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.81 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.4 (C=), 141.1 (=CH), 133.2 (C=), 129.7 (=CH), 126.1 (=CH), 112.2 (=CH_2), 71.2 (CHOH), 71.1 (C), 66.7 (CHOH), 49.8 (CH), 49.4 (CH), 45.1 (CH_2), 44.3 (CH_2), 42.8 (CH_2), 38.5 (CH), 34.1 (CH_2), 32.4 (CH), 30.5 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 26.2 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 18.6 (CH_3), 17.3 (CH_3) ppm. IR: $\tilde{\nu}$ = 3349 (s), 2931 (vs), 2862 (s), 1455 (m), 1377 (s), 1306 (m), 1208 (m), 1139 (m), 1101 (m), 1053 (vs), 1028 (vs), 976 (vs), 959 (m), 911 (s), 928 (vs), 877 (w), 756 (w), 736 (vs) cm^{-1}. MS: m/z (%) = 372 (7), 336 (3), 243 (1), 207 (1), 164 (14), 148 (50), 131 (36), 105 (25), 95 (42), 59 (100), 49 (34).

5b: R_f = 0.74 (acetone). $[\alpha]_D$ = +24.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.33 (dd, J = 15.1, 10.7 Hz, 1 H), 6.03 (d, J = 10.7 Hz, 1 H), 5.53 (dd, J = 15.1, 8.8 Hz, 1 H), 5.30 (s, 1 H), 4.99 (s, 1 H), 4.43 (m, 1 H), 4.21 (m, 1 H), 2.57 (d, J = 12.9 Hz, 1 H), 2.25 (dd, J = 12.9, 7.5 Hz, 1 H), 1.96 (m, 2 H), 1.78 (m, 1 H), 1.74 (m, 1 H), 1.64 (m, 4 H), 1.53 (m, 1 H), 1.44 (t, J = 8.1 Hz, 2 H), 1.32 (m, 2 H), 1.24 (m, 1 H), 1.21 (s, 6 H), 1.19 (m, 1 H), 1.08 (m, 2 H), 0.97 (m, 2 H), 0.80 (d, J = 6.3 Hz, 3 H), 0.72 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.4 (C=), 141.1 (=CH), 133.2 (C=), 129.7 (=CH), 126.0 (=CH), 112.2 (=CH_2), 71.2 (CHOH), 71.1 (C), 66.7 (CHOH), 49.3 (CH), 46.9 (CH), 45.1 (CH_2), 44.2 (CH_2), 42.8 (CH_2), 38.6 (CH), 36.2 (CH_2), 34.0 (CH_2), 32.2 (CH), 29.3 (CH_3), 29.2 (CH_3), 26.0 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 17.0 (CH_3), 13.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3354 (s), 2961 (s), 2924 (vs), 2853 (s), 1721 (vw), 1628 (vw), 1445 (m), 1377 (m), 1300 (m), 1212 (m), 1168 (m), 1150 (m), 1054 (s), 975 (m), 959 (m), 912 (m), 737 (m) cm^{-1}. MS: m/z (%) = 336 (14), 318 (4), 292 (3), 260 (4), 253 (11), 212 (4), 193 (8), 165 (5), 151 (18), 129 (100), 95 (52), 59 (52), 41 (22).

6a: R_f = 0.70 (acetone). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.37 (dd, J = 15.2, 10.8 Hz, 1 H), 6.02 (d, J = 10.8 Hz, 1 H), 5.66 (dd, J = 15.2, 7.2 Hz, 1 H), 5.31 (s, 1 H), 5.01 (s, 1 H), 4.43 (m, 1 H), 4.21 (m, 1 H), 2.56 (dd, J = 13.2, 1.8 Hz, 1 H), 2.26 (dd, J = 13.2, 6.8 Hz, 1 H), 1.97 (m, 3 H), 1.76 (m, 1 H), 1.69 (m, 2 H), 1.59 (s, 1 H), 1.54 (s, 1 H), 1.52 (m, 1 H), 1.45 (m, 2 H), 1.33 (m, 2 H), 1.22 (m, 9 H), 1.05 (m, 2 H), 0.99 (m, 1 H), 0.85 (d, J = 6.2 Hz, 3 H), 0.79 (q, J = 12.3 Hz, 1 H), 0.72 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.5 (C=), 141.1 (=CH), 133.6 (C=), 129.7 (=CH), 124.1 (=CH), 111.9 (=CH_2), 71.1 (C), 71.0 (CHOH), 66.8 (CHOH), 47.2 (CH), 45.0 (CH_2), 44.2 (CH_2), 42.8 (CH_2), 41.5 (CH), 36.0 (CH_2), 35.8 (CH_2), 33.8 (CH), 32.8 (CH_2), 32.3 (CH), 31.3 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 22.6 (CH_2), 19.7 (CH_3), 13.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3288 (m), 2925 (s), 2849 (m), 2161 (vw), 1979 (vw), 1636 (w), 1445 (m), 1376 (s), 1305 (m), 1245 (m), 1214 (m), 1166 (m), 1155 (m), 1047 (vs), 1034 (vs), 971 (s), 959 (vs), 912 (vs), 893 (m), 737 (s), 668 (s) cm^{-1}. MS: m/z (%) = 372 (7), 354 (3), 259 (3), 241 (2), 223 (2), 187 (1), 164 (11), 133 (19), 105 (15), 91 (25), 59 (100), 43 (39).

6b: R_f = 0.25 (*i*-octane/EtOAc, 1:1). UV (MeOH): λ = 205, 249 nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.37 (dd, J = 15.1, 10.9 Hz, 1 H), 6.02 (d, J = 10.9 Hz, 1 H), 5.65 (dd, J = 15.1, 7.1 Hz, 1 H), 5.31 (s, 1 H), 5.01 (s, 1 H), 4.43 (m, 1 H), 4.21 (m, 1 H), 2.66 (dd, J = 13.3, 3.5 Hz, 1 H), 2.26 (dd, J = 13.3, 7.0 Hz, 1 H), 1.96 (m, 3 H), 1.76 (m, 1 H), 1.69 (m, 2 H), 1.62 (m, 1 H), 1.43 (m, 3 H), 1.29 (m, 9 H), 1.05 (m, 2 H), 0.91 (m, 1 H), 0.89 (d, J = 7.3 Hz, 3 H), 0.86 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6 (C=), 141.4 (=CH), 133.7 (C=), 129.8 (=CH), 124.2 (=CH), 112.0 (=CH_2), 71.2 (C), 71.1 (CHOH), 66.8 (CHOH), 50.0 (CH), 45.1 (CH_2), 44.3 (CH_2), 42.9 (CH_2), 41.7 (CH), 36.0 (CH_2), 33.7 (CH), 32.9 (CH_2), 32.5 (CH), 32.3 (CH_2), 30.7 (CH_2), 29.3 (CH_3), 29.2 (CH_3), 20.1 (CH_2), 20.0 (CH_3), 18.4 (CH_3) ppm. IR: $\tilde{\nu}$ = 3349 (s), 2920 (vs), 2868 (s), 1454 (m), 1370 (m), 1305 (w), 1269 (w), 1207 (w), 1150 (w), 1055 (s), 975 (m), 961 (m), 915 (m), 736 (m) cm^{-1}. MS: m/z (%) = 372 (2), 336 (10), 288 (3), 232 (4), 202 (2), 149 (14), 129 (77), 91 (58), 59 (100).

7a: R_f = 0.40 (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.36 (dd, J = 15.4, 10.8 Hz, 1 H), 6.02 (d, J = 10.8 Hz, 1 H), 5.66 (dd, J = 15.4, 7.0 Hz, 1 H), 5.31 (s, 1 H), 5.01 (s, 1 H), 4.43 (m, 1 H), 4.21 (m, 1 H), 2.56 (dd, J = 13.3, 3.7 Hz, 1 H), 2.26 (dd, J = 13.3,

7.0 Hz, 1 H), 1.99 (m, 1 H), 1.96 (m, 2 H), 1.92 (m, 1 H), 1.56 (m, 2 H), 1.54 (d, J = 4.9 Hz, 1 H), 1.50 (d, J = 5.3 Hz, 1 H), 1.42 (m, 6 H), 1.25 (m, 3 H), 1.21 (s, 6 H), 1.15 (m, 1 H), 1.05 (m, 1 H), 0.90 (q, J = 12.5 Hz, 1 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6 (C=), 141.5 (=CH), 133.6 (C=), 129.8 (=CH), 124.1 (=CH), 112.0 ($=CH_2$), 71.1 (CHOH), 71.0 (C), 66.8 (CHOH), 45.1 (CH_2), 45.0 (CH), 44.4 (CH_2), 42.9 (CH_2), 41.9 (CH), 34.4 (CH), 34.1 (CH_2), 33.5 (CH_2), 30.6 (CH_2), 29.4 (CH_3), 29.3 (CH_3), 28.6 (CH), 26.6 (CH_2), 21.1 (CH_2), 17.4 (CH_3), 12.3 (CH_3) ppm.

7b: R_f = 0.40 (EtOAc). UV (MeOH): λ = 207, 249 nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.37 (dd, J = 15.5, 10.7 Hz, 1 H), 6.03 (d, J = 10.7 Hz, 1 H), 5.68 (dd, J = 15.5, 6.9 Hz, 1 H), 5.31 (s, 1 H), 5.01 (s, 1 H), 4.44 (m, 1 H), 4.22 (m, 1 H), 2.57 (dd, J = 13.2, 1.9 Hz, 1 H), 2.26 (dd, J = 13.2, 6.9 Hz, 1 H), 1.99 (m, 1 H), 1.97 (m, 2 H), 1.93 (m, 1 H), 1.70 (s, 1 H), 1.61 (m, 2 H), 1.51 (s, 1 H), 1.49 (m, 1 H), 1.43 (m, 5 H), 1.22 (m, 9 H), 1.13 (m, 1 H), 1.05 (m, 1 H), 0.90 (q, J = 12.3 Hz, 1 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6 (C=), 141.4 (=CH), 133.7 (C=), 129.8 (=CH), 124.2 (=CH), 111.9 ($=CH_2$), 71.2 (COH), 71.0 (CHOH), 66.8 (CHOH), 45.1 (CH_2), 45.1 (CH), 44.4 (CH_2), 42.9 (CH_2), 41.8 (CH), 34.8 (CH), 34.8 (CH_2), 33.5 (CH_2), 30.6 (CH_2), 29.3 ($2\times CH_3$), 28.5 (CH), 26.7 (CH_2), 21.5 (CH_2), 17.0 (CH_3), 11.9 (CH_3) ppm. IR: $\tilde{\nu}$ = 3358 (m), 2966 (vs), 2922 (vs), 2853 (s), 1724 (vw), 1628 (vw), 1445 (m), 1378 (m), 1225 (m), 1155 (m), 1050 (s), 975 (m), 956 (m), 914 (s), 754 (s) cm^{-1}. MS: m/z (%) = 372 (3), 259 (2), 241 (2), 223 (1), 175 (1), 164 (8), 146 (21), 105 (19), 91 (31), 59 (100), 43 (36).

X-ray Structure Determination: Single-crystal diffraction data were collected with an Oxford Xcalibur CCD area detector diffractometer by using graphite monochromatic Mo-K_α (λ = 0.71069 Å) radiation. Data reduction and absorption correction were performed by using CrysAlis RED 1.171.26 (Oxford Diffraction). The structure was solved by direct methods with the use of SIR2004[27] and refined by full-matrix least-squares by using SHELX-97.[28] Hydrogen atoms were generated in calculated position by using SHELX-97. CCDC-710052 (for **15**) and -710053 (for **14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conformational Analysis and Molecular Modeling: Conformational analysis of the side chain of compounds **5a**, **5b**, **6a**, **6b**, **7a**, and **7b** was carried out by using the MacroModel molecular modeling program of Still[29] run on a Digital VAXstation 4000–90A or SiliconGraphics Octane. Molecular mechanics calculations were carried out on model compounds in which the A-ring and diene system up to C6 were replaced by an H atom. Rotations with 60° increments were applied to the rotatable C–C bonds of the side chain, whereas the 25-OH was rotated with increments of 120°. The so-generated starting conformations were minimized by using the MM2* force-field implementation of MacroModel and the conformations within 20 kJ mol^{-1} of the minimum energy form were retained. With the use of a PC computer program all conformations of each compound were then overlaid by using C13 as common origin (x, y, z = 0), C14 was positioned in the yz-plane (x = 0) and the 18-position was made to coincide with the positive y axis (x, z = 0). A line drawing was generated of the minimum energy conformation and the position of O25 in each of the local energy minima within the given energy window was represented by a ball to obtain the volume maps shown in Figure 12.

Biological Evaluation – Binding Studies: The affinity of the 6D analogues of $1,25(OH)_2D_3$ to the vitamin D receptor was evaluated by their ability to compete with [3*H*]$1,25(OH)_2D_3$ for binding to high-speed supernatant from intestinal mucosa homogenates obtained from normal pigs as described previously.[30] The relative affinity of the analogues was calculated from their concentration needed to displace 50% of [3*H*]$1,25(OH)_2D_3$ from its receptor compared with the activity of $1,25(OH)_2D_3$.

Biological Evaluation – MCF-7 Proliferation Assay: The human breast carcinoma (MCF-7) cell line was obtained from the American Tissue Culture Company (Rockville, MD). The antiproliferative activity of $1,25(OH)_2D_3$ or 6D analogues on MCF-7 cells was assessed by evaluating [^{3}H]thymidine incorporation. Cells were seeded in 96-well plates (7500 cells/well) and 1 μCi [methyl-^{3}H]-thymidine (ICN Biomedicals, Costa Mesa, CA) was added 72 h after the initiation of treatment. Cells were semi-automatically harvested after an additional 6 h of incubation on filter plates only retaining incorporated thymidine (GF/C Filter and Filtermate Universal Harvester, Packard Instrument, Meriden, CT). Counting was performed by using a microplate scintillation counter (Topcount, Packard).

Biological Evaluation – In Vivo Studies: NMRI mice were obtained from the Proefdierencentrum of Leuven (Belgium) and fed on a vitamin D-replete diet (0.2% calcium, 1% phosphate, 2000 U vitamin D kg^{-1}; Hope Farms, Woerden, The Netherlands). The hypercalcemic effect of the 6D analogues was tested in NMRI mice by daily subcutaneous injection of $1,25(OH)_2D_3$, its analogues or the solvent during 7 consecutive days by using serum calcium concentration as parameter.

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