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Novel versatile approach to an enantiopure 19-*nor*, *des*-C,D vitamin D_3 derivative☆

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Abstract—A short and efficient *de novo* route to the *des*-C,D vitamin D_3 derivative **3** (Ro 65-2299), a potential antipsoriatic, has been developed. This route features an assembly strategy so far unexplored in vitamin D chemistry involving a modified Julia olefination of the A-ring ketone **30** and the 2-benzothiazolyl sulfone **60**. Construction of the A-ring building block was accomplished by an efficient three-step route starting from the *meso trans*-1,3,5-cyclohexane triol (**26**), which was desymmetrized by a highly selective enzymatic mono-hydrolysis of the corresponding triacetate **27** followed by oxidation of the alcohol **29** to give the homochiral diacetoxy ketone **30** (ee=99.5%) in 83% overall yield. Furthermore, we found efficient and practical syntheses of the 5-acetoxy-2-cyclohexenone (**31**) and its enantiomer **32**, both new building blocks useful for natural product synthesis.

[1]Introduction

Vitamin D research has attracted much attention in recent years with the finding that calcitriol **1** (Fig. 1), the pharmacologically active metabolite of vitamin D_3, exhibits a far broader activity beyond regulating calcium and phosphorus metabolism.[1,2] As a result, structurally modified compounds are currently being explored extensively, e.g. in the area of oncology,[3] bone diseases,[4] and skin diseases.[5] A recent and hardly explored modification first published by Kutner et al.[6] involves the retiferol **2**, a compound that lacks the C,D-ring substructure. Based on molecular modelling, Kutner hypothesised that for receptor binding the 3D arrangement of the three hydroxy groups should be sufficiently preserved. Subsequently, Mohr et al.[7] from Roche, Basel, prepared a variety of *des*-C,D vitamin D_3 derivatives from which the compounds with terminal CF_3 groups showed improved activities. The molecular structure was

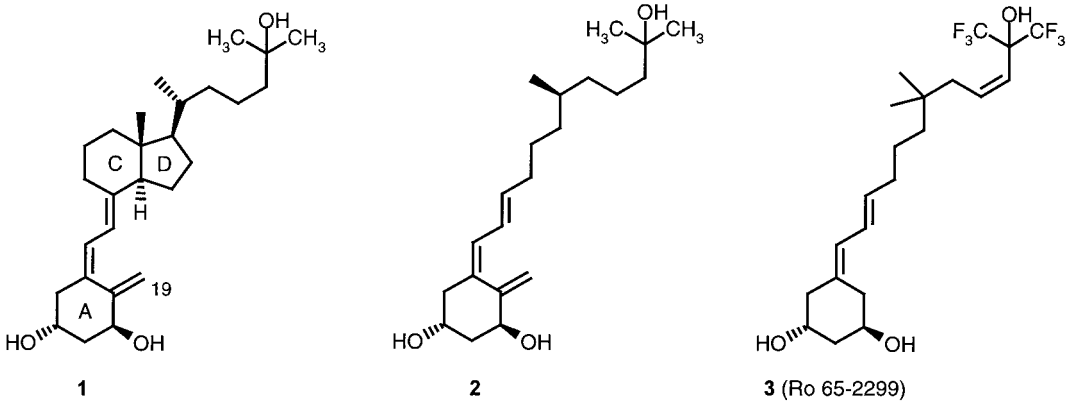

Figure 1. Selected structures of vitamin-D_3 derivatives.

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Keywords: cyclohexanones; enzyme reactions; sulfones; vitamins.

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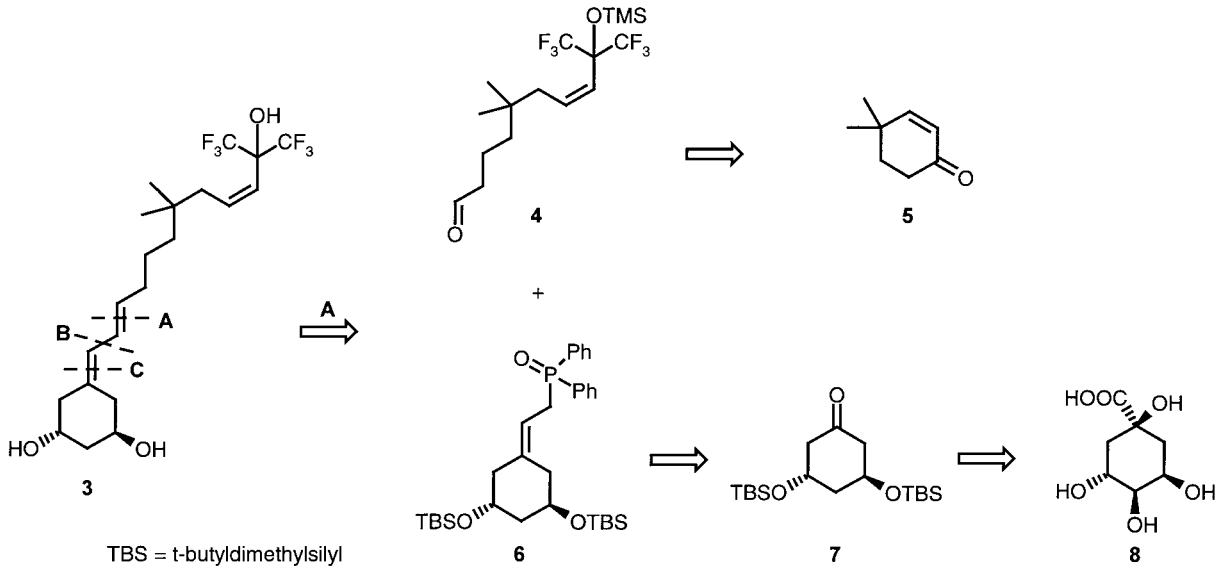
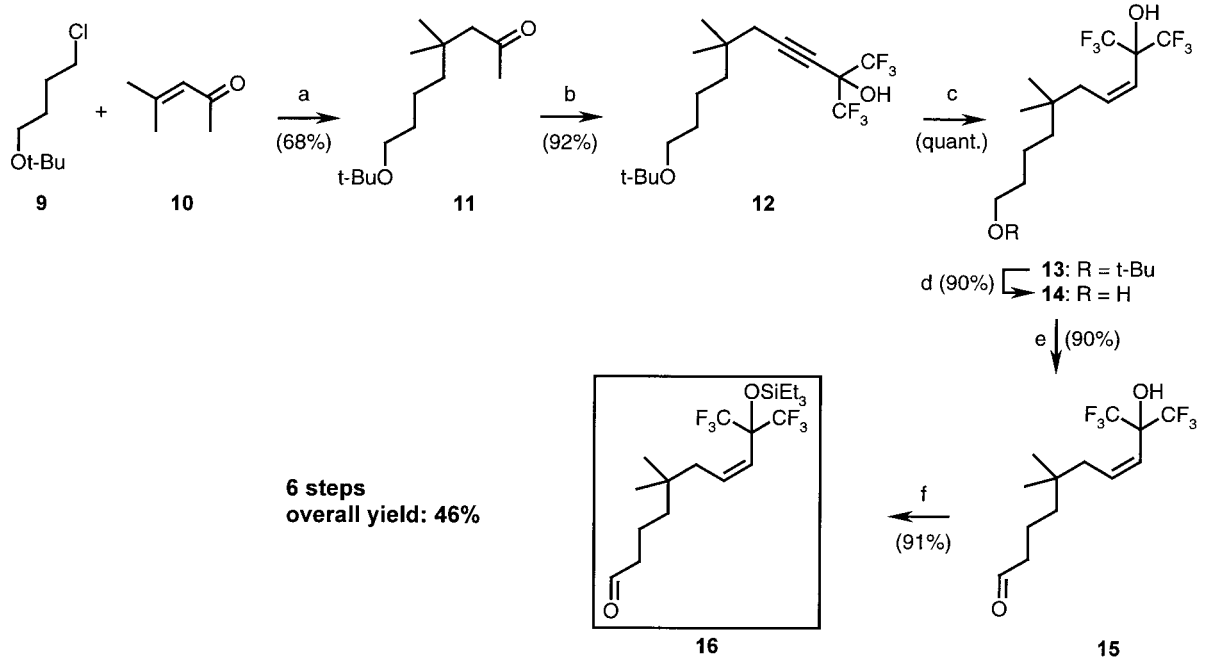


Scheme 1. Retrosynthesis of the retiferol **3**.

further modified in the side chain and simplified in the A-ring segment by omitting the exocyclic methylene group finally leading to the 19-*nor*, *des*-C,D vitamin D_3 derivative **3**, a compound to be considered as a locked vitamin D_3 analogue incapable of equilibrating with the corresponding pre-vitamin.[8] Retiferol **3** (Ro 65-2299) represents a potent activator of the vitamin D receptor hardly displaying any undesired hypercalcemia relevant for therapeutic applications, and was therefore selected as a clinical candidate for the evaluation of a potential oral therapy for psoriasis.

Various syntheses of 19-*nor* analogues are documented in the literature.[9,10] In all cases the diene substructure has been introduced by the disconnection **A** (Scheme 1) leading to the key intermediate phosphinoxide **6** and the corresponding carbonyl building block. For the retiferol **3**, the required TMS-protected aldehyde **4** was prepared in 11 steps starting from 4,4-dimethyl-2-cyclohexenone (**5**).[7] Three routes to the phosphinoxide **6** are known in the literature, the shortest one developed by DeLuca[9] involving a ten-step synthesis starting from (−)-quinic acid (**8**) (overall yield 13%). More recently Mikami[11] and Uskokovic[12] published elegant 13- and 12-step syntheses, respectively, starting from achiral acyclic precursors (overall yields 6% and 14%, respectively). Both routes are based on a highly stereoselective carbonyl-ene cyclization as the key steps.



Scheme 2. *Reagents and conditions:* (a) (i) **9**, Mg, THF, 65°C, 3.5 h; (ii) $CuI_{cat.}$, **10**, THF, −20°C, 1 h; (b) (i) LDA, diethyl chlorophosphate, THF, −78 to 22°C, 2 h; (ii) LDA, hexafluoro acetone, −78°C, 30 min; (c) H_2 (1 bar), $Pd/CaCO_3/Pb$ (4.5%), *tert*-butyl methyl ether, 22°C, 1.5 h; (d) H_2SO_4, H_2O/*i*-PrOH, 80°C, 2 h; (e) NaOCl, $TEMPO_{cat.}$, CH_2Cl_2/H_2O, 0°C, 1 h; (f) Et_3SiCl, NEt_3, $DMAP_{cat.}$, THF, 22°C, 1.5 h.

Due to our interest in the clinical development of retiferol **3**, we evaluated new routes to the aldehyde **4** and to the phosphinoxide **6** via a suitably protected ketone **7**. In addition, alternative coupling strategies (**B**- and **C**-disconnections) requiring a facile preparation of the corresponding A-ring precursors were also considered. Herein, we report an efficient and practical route to both enantiomers of the phosphinoxide **6** and to the retiferol **3** based on enzymatic transformations and on a new coupling strategy. Furthermore, as a result of our investigations, short and high yielding routes to both enantiomers of the 5-acetoxy-2-cyclohexenones (**31**) and (**32**), versatile building blocks for natural product synthesis were also discovered.

2. Results and discussion

2.1. Synthesis of the aldehyde side-chain 16

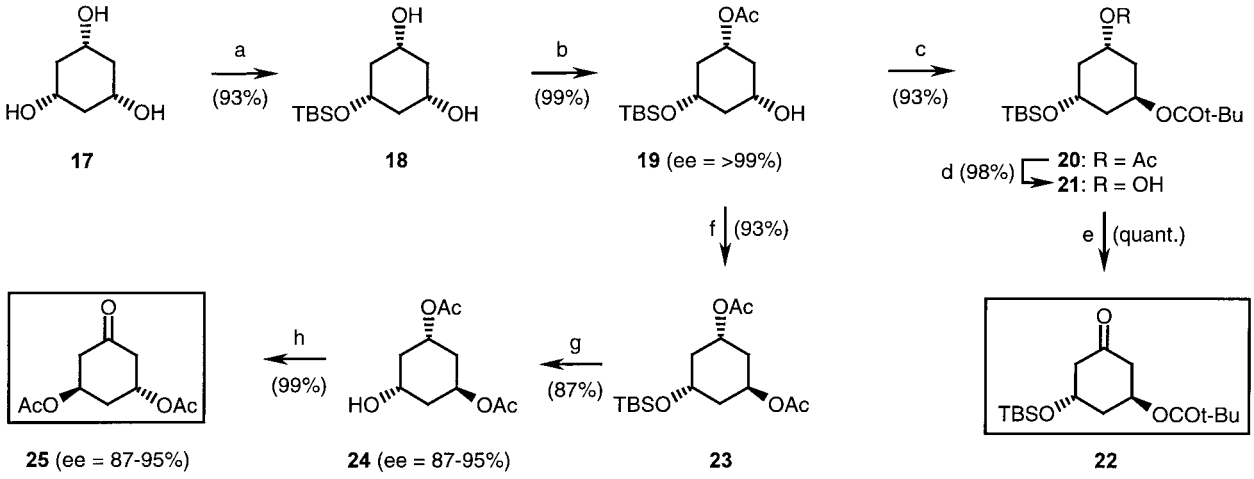
A convenient route to the aldehyde side-chain **16** incorporating the more stable triethylsilyl protecting group compared to TMS (Scheme 2) was elaborated. The Grignard reagent derived from 1-*tert*-butyloxy-4-chloro-butane (**9**)[13] was subjected to a conjugate addition to mesityl oxide (**10**) furnishing the ketone **11** in 68% yield. Dehydration of **11** was accomplished via in situ formation of the enol phosphate[14] followed by trapping of the intermediate alkyne lithium species with hexafluoro acetone affording the alkyne **12** in good yield (92%). Hydrogenation of the triple bond in **12** with Lindlar's catalyst proceeded with high diastereoselectivity to give a 98.6:1.4 mixture in favour of the *Z*-configurated alkene **13**, which was deprotected to the diol **14** in a 90% overall yield (from **12**).

Oxidation of the primary alcohol group in **14** was readily accomplished by a TEMPO[15] catalysed bleach oxidation providing the aldehyde **15** in good yield (90%). In search of a more stable protecting group the pivaloyl, *tert*-butyldimethylsilyl and the triethylsilyl groups were evaluated, but only the latter could be installed with Et_3SiCl/DMAP in dichloromethane to give the protected aldehyde **16** in a modest yield of 60%. A remarkable ten-fold acceleration of the reaction was achieved in THF yielding **16** in a 91%. This completed the short 6-step route of the side chain affording a good overall yield of 46% of the protected aldehyde **16** with minimal purification operations of the intermediates involving only two chromatographic separations and one crystallization.

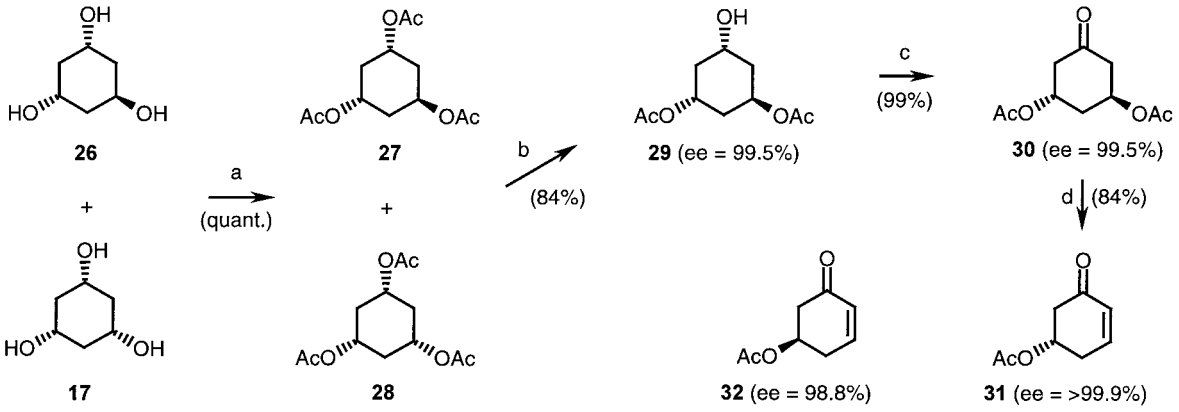
2.2. Facile synthesis of the phosphinoxide 6 and its enantiomer 40

In search of a shorter route to a suitably protected ketone **7** (Scheme 1), we evaluated an enzyme catalysed desymmetrization of the *meso*-diol **18** (Scheme 3) to the mono acetate **19**. The selective and high yielding protection (84%) of the *cis*-triol **17** to the mono TBS-ether **18** reported in the literature[16] was not reproducible in our hands due to the lack of selectivity leading also to the *bis*- and *tris*-TBS ethers. High yield and selectivity, however, was achieved using a mixture of NaH and NEt_3 as the bases, the latter one inducing a significant acceleration of the reaction thus enhancing the selectivity, although the role of NEt_3 is not fully understood. This process reproducibly provided **18** in a high yield of 93% after crystallization on a 70 g scale. Asymmetric acylation of the *meso*-diol **18** was extensively investigated by Wirz et al.[17] involving a broad panel of commercially available enzymes. Lipase QL from Meito Sangyo proved to be the most rapid catalyst furnishing the required enantiomer (vide infra) of the alcohol **19** in a quantitative yield and high enantiomeric purity (ee=>99%). Alcohol **19** served as a common intermediate to synthesise the desired ketone **22** and its diacetyl protected enantiomer **25**, representing potential new intermediates of general interest and expanding the scope of preparing vitamin D analogues. Thus, the configuration of the hydroxy group in **19** was inverted by Mitsunobu reaction affording the fully protected pivaloate **20**, which was selectively deacetylated and oxidised with bleach to give the ketone **22** in a high overall yield (90% from **19**).

Alternatively, the Mitsunobu reaction of **19** with acetic acid provided the diacetate **23**, which after cleavage of the *tert*-butyldimethylsilyl protecting group with TBAF furnished



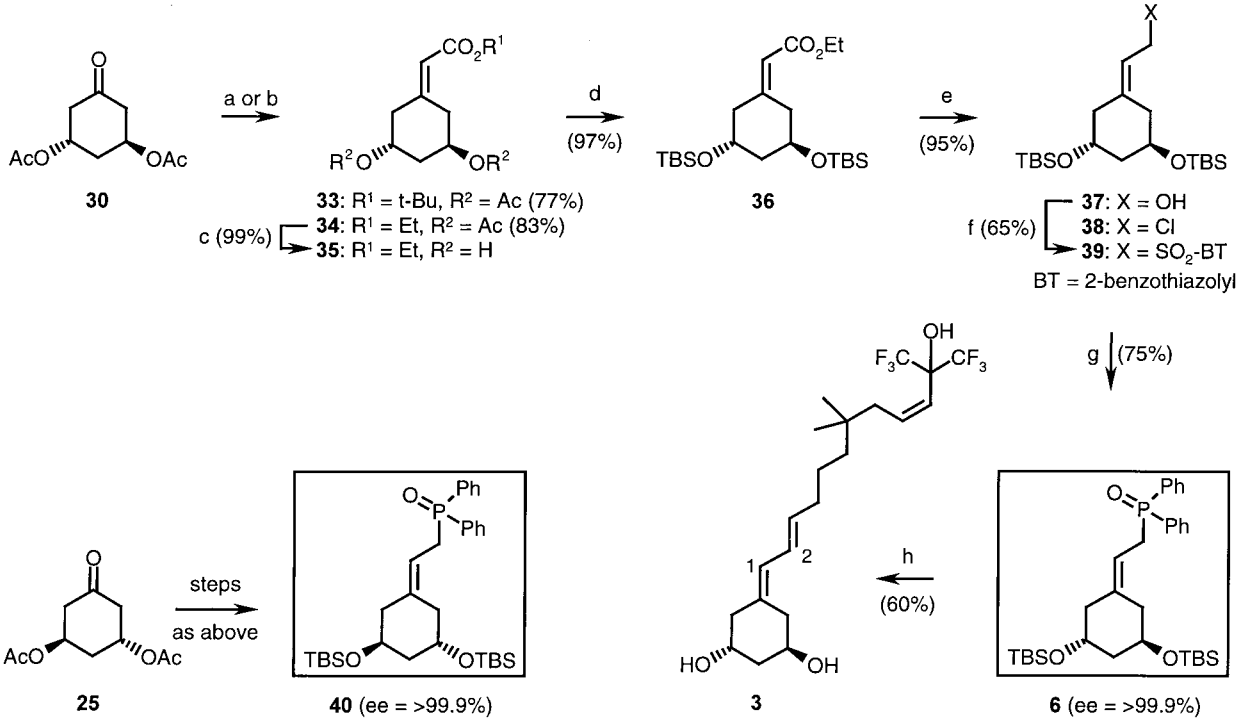
Scheme 3. *Reagents and conditions:* (a) TBSCl, NaH, NEt_3, THF, 40°C, 2 h; (b) Lipase QL, vinyl acetate, AcOEt, 22°C, 46 h; (c) PPh_3, *i*-$PrO_2CN{=}NCO_2$*i*-Pr, *tert*-$BuCO_2H$, THF, 0°C, 1 h; (d) K_2CO_3, MeOH/H_2O, 22°C, 7 h; (e) NaOCl, $TEMPO_{cat.}$, CH_2Cl_2/H_2O, 0°C, 1 h; (f) PPh_3, *i*-$PrO_2CN{=}NCO_2$*i*-Pr, AcOH, THF, 0°C, 2 h; (g) TBAF (1 M, THF), THF, 0°C, 3 h; (h) NaOCl, $TEMPO_{cat.}$, CH_2Cl_2/H_2O/HCl, pH 6.5 −7.5, 0°C, 1 h.



Scheme 4. *Reagents and conditions:* (a) Ac_2O, pyridine, 45°C, 4 h, 77:18 mixture of **27** and **28**; (b) Lipase OF, cyclohexane, NaOH/H_2O, pH 7.0, 5–6°C, 21.5 h; (c) NaOCl, $TEMPO_{cat.}$, CH_2Cl_2/H_2O/HCl, pH 6.5 −7.5, 0°C, 1 h; (d) Al_2O_3, THF, 22°C, 1 h.

the alcohol **24** in good yield (87%) but lower enantiomeric excess of 87–95%. This partial racemization is attributable to a 1,3-migration of the acetyl group located *cis* to the hydroxy group in **24**. Bleach/TEMPO oxidation of the alcohol **24** under pH control (vide infra) finally provided access to the ketone **25** (ee=87–95%) in a 80% overall yield from **19**. The enantiomeric purity of **25** was sufficient for further processing since improvements were observed for later stage intermediates. Alternatively, the enantiomeric purity was improved to an ee of 99% by a single crystallization.

An even shorter route to the enantiomeric diacetoxy ketone **30** (Scheme 4) is based on the selective enzymatic hydrolysis of the *trans*-triacetate **27** to the *trans*-diacetate **29**. *trans*-Cyclohexane-1,3,5-triol (**26**), commercially available from Tokyo Kasei as a 1:1 mixture of the *trans*- and *cis*-triol **26** and **17**, was prepared by hydrogenation of 1,3,5-trihydroxy benzene.[18] A one-pot method providing an improved 2:1 mixture of **26** and **17** was recently presented by Roessler et al.[19] involving the Raney nickel catalysed hydrogenation of 1,3,5-trihydroxy benzene and subsequent isomerization of the *cis*-triol **17** to the thermodynamically more stable *trans*-isomer **26** at elevated temperature. The *trans*-isomer **26** was further enriched by preferential crystallization of the *cis*-triol **17** from ethanol/water affording a



Scheme 5. *Reagents and conditions:* (a) **33**: $TMSCH_2CO_2$*tert*-Bu, LDA, THF, −78°C, 15 min, then **30**, −78°C, 2 h; (b) **34**: $TMSCH_2CO_2Et$, LDA, THF, −78°C, then **30**, −78°C, 1.5 h; (c) K_2CO_3, MeOH/H_2O, 22°C, 6 h; (d) TBSCl, imidazole, DMF, 22°C, 3 h; (e) Red-Al®, toluene, −15°C, 1 h; (f) (i) 2-mercaptobenzothiazole, PPh_3, then **37**, *i*-$PrO_2CN{=}NCO_2i$-Pr, THF, 0°C, 30 min; (ii) H_2O_2/H_2O, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O_{cat.}$, EtOH, 22°C, 10 h; (g) (i) **37**, *n*-BuLi, THF, 0°C, then TsCl, 0°C, 2.5 h; (ii) $HPPh_2$, *n*-BuLi, THF, 0°C, 1 h; (iii) H_2O_2, CH_2Cl_2/H_2O, 22°C, 3.5 h; (h) (i) **6**, *n*-BuLi, THF, −78°C, 30 min; (ii) **16**, −78 to 22°C, 64 h; (iii) TBAF (1 M, THF), 45°C, 12 h; (iv) HPLC, Kromasil 10–100, heptane/*i*-PrOH 92:8.

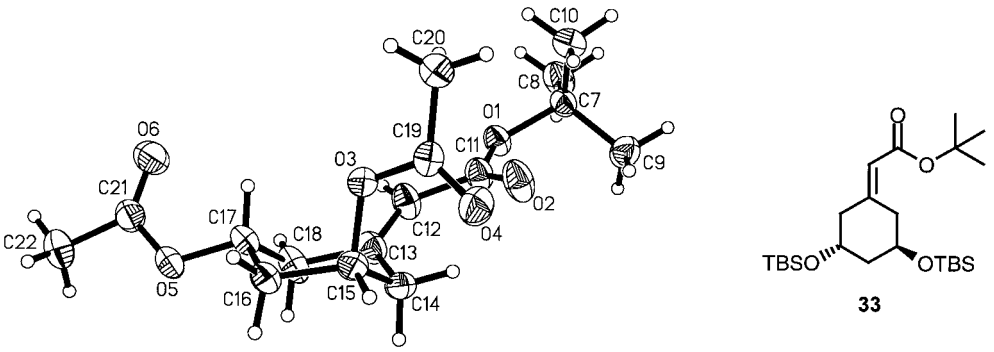


Figure 2. Monoview of the *tert*-butyl ester **33** with thermal ellipsoids at 20% probability level.

mother liquor containing a 4:1 mixture favouring the *trans*-triol **26**.

The conversion of the *meso trans*-1,3,5-triacetoxy cyclohexane (**27**) to the homochiral diacetate **29** requires the selective enzymatic hydrolysis of only one of the three stereo-different acetoxy groups and limitation to monohydrolysis. Futhermore, the identification of an enzyme preventing at the same time the hydrolysis of the *cis*-triacetate **28** completely would easily allow the separation of the desired product **29** from unreacted **28** after the enzymatic reaction. Surprisingly, these highly demanding selectivity requirements were achieved by using cheap lipase OF ($15/kg **29**) isolated from *Candida rugosa* as demonstrated by Wirz et al.[17] providing the desired diacetate enantiomer **29** (vide infra) in high enantiomeric excess of 99.5% and good yield (84%, based on *trans*-**26** present in the mixture) after chromatographic filtration of the reaction mixture. Oxidation of the alcohol **29** to the ketone **30** with bleach/TEMPO proved to be highly sensitive to the basic conditions resulting in an approximately 9:1 mixture of the ketone **30** and the enone **31**. However, the formation of **31** was completely suppressed by keeping the pH at 7 during addition of the bleach furnishing the crystalline ketone **30** in quantitative yield, which is stable at −20°C for months but slowly decomposes at ambient temperature.

The remarkable stability of the enone **31** towards aromatization under basic conditions not instantly leading to phenol prompted us to investigate the preparation of the chiral 5-acetoxy enone **31**, an unknown building block potentially useful for natural product synthesis.[20] Various chiral 5-substituted 2-cyclohexenones are known in the literature including the trimethylsilyl,[21,22] the benzyloxy[23,24] and the *tert*-butyldimethylsilanyloxy[20] derivative, the latter one extensively investigated by Sato et al. Conversion of the diacetoxy ketone **30** to the acetoxy enone **31** was investigated with various bases, basic alumina proving to be the base of choice affording **31** in 84% yield. Preliminary results indicated that **31** undergoes conjugate additions of higher- and lower-order cuprates with *trans*- and *cis*-selectivity, respectively, as recently described by Sato et al.[20] for the corresponding *tert*-butyldimethylsilanyloxy derivative. As an unexpected extension of our investigations, this new chiral building block **31** is now readily accessible from cheap **26** in four steps and a high overall yield of 70%. In addition, the enantiomeric enone **32** was also prepared from the diacetoxy ketone enantiomer **25** (ee=87%) in 70% yield and 98.8% ee after crystallization from *tert*-butyl methyl ether.

With the short and high yielding synthesis of the diacetoxy ketone **30** (three steps, 83% overall from **26**) at hand we developed a practical route to the phosphinoxide **6** and its enantiomer **40** as outlined in Scheme 5 in analogy to the chemistry developed by DeLuca.[9]

Peterson olefination of **30** with *tert*-butyl- or ethyl-trimethylsilyl-acetate provided the esters **33** and **34**, respectively. The crystalline *tert*-butyl ester **33** was used to determine the absolute configuration by X-ray analysis (Fig. 2)[25] which in turn allowed now to assign the absolute configuration of the alcohols **19** and **29** resulting from the enzymatic reactions (vide supra): Since the *tert*-butylester **33** was prepared from the alcohol **29**, the absolute configuration of **29** is also confirmed. In addition, the alcohol **19** was converted to the alcohol **24**, spectroscopically identical to **29** but clearly separated from **29** on a chiral GLC column (BGB-175). This corroborates the enantiomeric relationship of the two compounds and therefore allows the assignment of the absolute configuration of the alcohol **19**.

Removal of the acetoxy groups in the ester **34**, not resistant to the forthcoming reducing conditions (**36**→**37**), was achieved with K_2CO_3 in MeOH/H_2O providing the ethyl ester **35** in good yield (82%, from **30**) containing approximately 25% of the corresponding methyl ester formed by partial *trans*-esterification with MeOH. All attempts, however, to replace MeOH by EtOH resulted in a sluggish reaction. Reprotection of the hydroxy groups in **35** as the TBS ether **36** and subsequent reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) furnished the allylic alcohol **37** in excellent yield (92% from **35**). This material was converted to the phosphinoxide **6** via in situ formation of the labile allyl tosylate in analogy to a method developed by DeLuca et al.[26] thus avoiding the isolation of the hitherto used allyl chloride **38**,[9] which in our hands proved to be unstable during chromatography on a larger scale. Likewise, the enantiomeric ketone **25** was converted to the new phosphinoxide enantiomer **40**. Both enantiomers **6** and **40** were obtained in a high enantiomeric purity of >99.9% after crystallization as determined by chiral HPLC. In summary, phosphinoxide **6** is now available in only eight steps and 47% overall yield comparing favourably with all methods (vide supra) known up to date.

2.3. Final assembly of the aldehyde 16 with the phosphinoxide 6

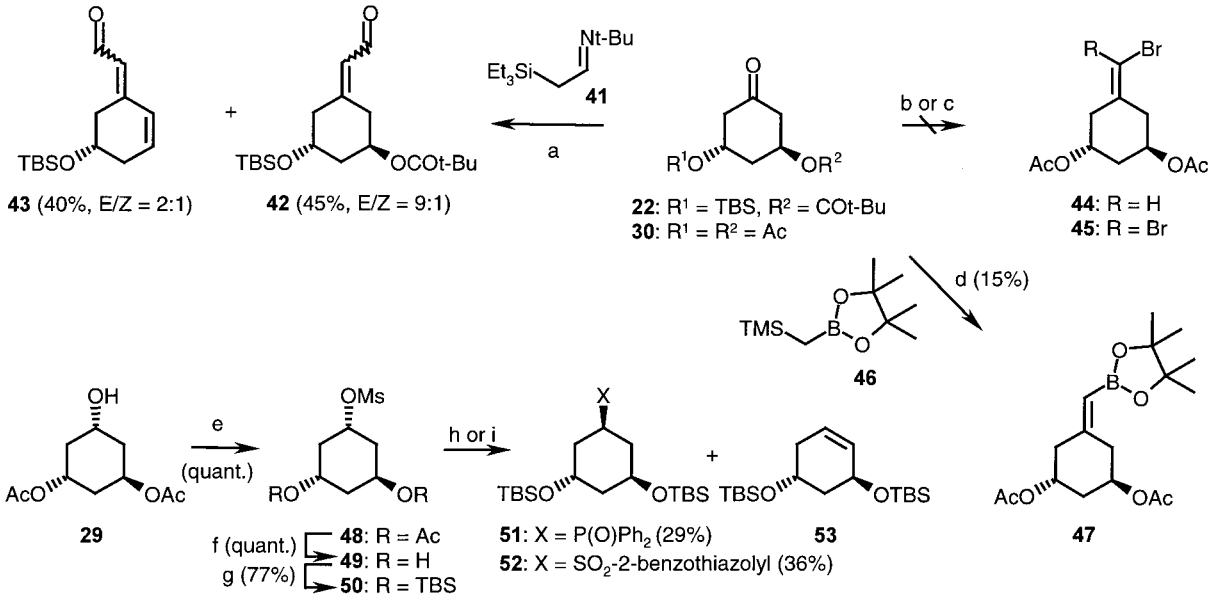
For the assembly of the side chain **16** with the A-ring segment (Scheme 5) we evaluated a modified Julia olefination[27–29] involving the sulfone **39** and the Horner reaction[9,30] employing the phosphinoxide **6**. The sulfone **39** was prepared from the allyl alcohol **37** by Mitsunobu reaction with 2-mercaptobenzothiazole[31,32] and subsequent ammonium heptamolybdate tetrahydrate catalysed oxidation[32,33] of the thioether intermediate using hydrogen peroxide. The coupling of **39** or **6** with the aldehyde **16** using *n*-BuLi at −78°C provided the expected intermediate diene as a mixture of partly deprotected intermediates. This mixture was subjected to TBAF conditions providing the retiferol isomers (2*E*)- and (2*Z*)-**3** as a 7:3 and 9:1 mixture, respectively, as determined by HPLC. Obviously, the highest selectivity was obtained with the phosphinoxide activating group originally developed by Lythgoe et al.[30] Separation of the isomers was not straightforward requiring a tedious HPLC chromatography yielding isomerically pure (2*E*)-retiferol **3** in approximately 60% yield (from **6**) as a resin.

2.4. Alternative coupling strategies

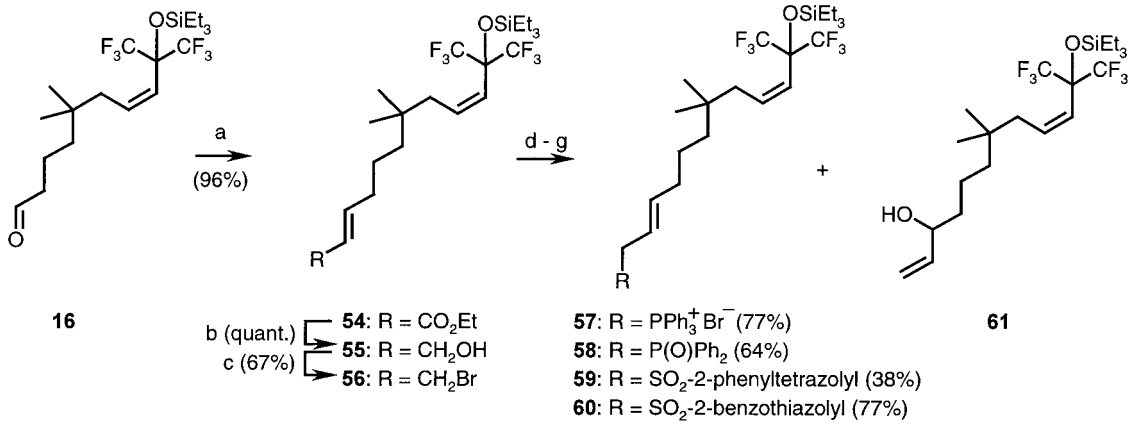
The modest yield of the olefination step and the cumbersome HPLC purification of the retiferol **3** prompted us to evaluate alternative coupling strategies such as the disconnection **A** with 'inverted' functional groups (Scheme 1) and the disconnections **B** and **C**. Expedient routes to the more complex A-ring building blocks were first evaluated starting from the ketones **22** and **30** (Scheme 6).

Olefination of the A-ring ketone precursor **22** with *N*-*tert*-butyl-2-(triethylsilyl)acetaldimine (**41**)[34,35] gave the desired exocyclic enal **42** as a 9:1 mixture of *E*- and *Z*-isomers but only in a poor yield of ca. 45% along with the dienal **43** (*E*/*Z*=2:1, 40%) resulting from elimination of pivalic acid. An exploratory investigation attempting a Suzuki coupling (disconnection **B**) was also undertaken, requiring the vinyl bromide **44** (or dibromide **45**) or the pinacol alkeneboronate **47**. Attempts to prepare compounds **44** or **45** with bromomethyltriphenyl phosphonium bromide or PPh_3/CBr_4, respectively, resulted in complex product mixtures. The reaction of the diacetoxy ketone **30** and pinacol (trimethylsilyl)methaneboronate **46**[36] gave a mixture of the pinacol alkeneboronate **47** (15%) and the enone **31** (45%). With the only **C**-disconnection remaining, we tried to prepare the phosphinoxide **51** and the sulfone **52**. Thus, alcohol **29** was mesylated to **48** (quant.), followed by attempted displacement with $LiPPh_2$ and oxidation with H_2O_2. However, instead of the expected phosphinoxide formation, cleavage of one of the acetoxy groups of the mesylate **48** was observed. Therefore, mesylate **48** was deprotected to form the alcohol **49** and reprotected as the TBS ether **50** (77% overall), which upon the reaction with $LiPPh_2$ followed by oxidation with H_2O_2 furnished the phosphinoxide **51** in low yield (29%) together with the olefin **53** as the major component (65%). Likewise, the reaction of the TBS-protected mesylate **50** with the sodium salt of 2-mercaptobenzothiazole followed by oxidation with H_2O_2 afforded the sulfone **52** in low yield (36%) accompanied by the olefin **53** (35%). Exploratory experiments towards deprotonation of the phosphinoxide **51** or the sulfone **52** with *n*-BuLi at −78°C revealed that neither of the compounds was stable to strong bases.

Since all attempts functionalizing the sensitive A-ring ketones **22** or **30** proved unsuccessful so far we explored the challenging **C**-disconnection with 'inverted' functional groups requiring the diacetoxy ketone **30** and a C_2 elongated



Scheme 6. *Reagents and conditions:* (a) **41**, LDA, THF, 0°C, 15 min, then **22**, −90°C, 1 h; (b) **44**: $BrCH_2PPh_3^+Br^-$, *tert*-BuOK, THF, −78°C, 30 min, then **30**, −78°C, 2 h; (c) **45**: **30**, CBr_4, PPh_3, CH_2Cl_2, −15°C; (d) (i) **46**, *n*-BuLi, 2,2,6,6-tetramethylpiperidine, *N*,*N*,*N*′,*N*′-tetramethylethyldiamine, THF, 0°C, 3 h, then **30**, −78°C; (e) CH_3SO_2Cl, NEt_3, CH_2Cl_2, 0°C, 1 h; (f) K_2CO_3, $MeOH/H_2O$, 22°C, 5 h; (g) TBSCl, imidazole, DMF, 22°C, 24 h; (h) **51**: (i) **50**, $HPPh_2$, *n*-BuLi, THF, 0°C, 10 h; (ii) H_2O_2, CH_2Cl_2/H_2O, 22°C, 3 h; (i) **52**: (i) 2-mercaptobenzothiazole, NaH, DMF, 22°C, 15 min, then **50**, 110°C, 1 h; (ii) H_2O_2/H_2O, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O_{cat.}$, EtOH, 22°C, 10 h.

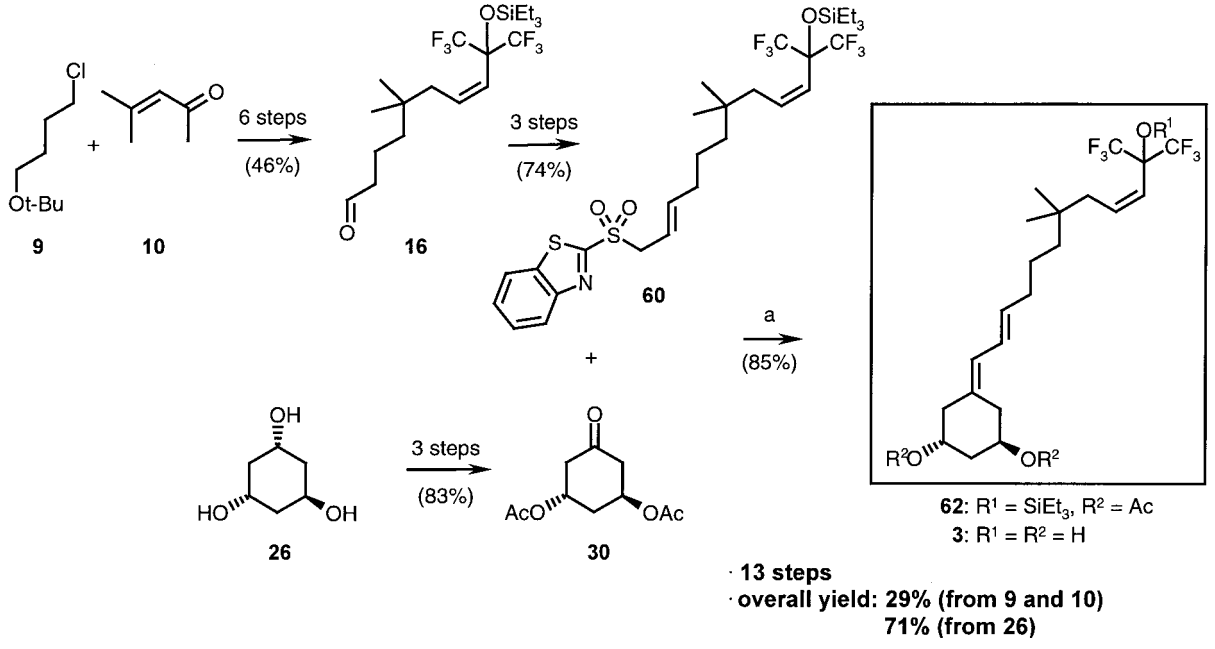


Scheme 7. *Reagents and conditions:* (a) $(EtO)_2P(O)CH_2CO_2Et$, *tert*-BuOK, toluene, 22°C, 1 h, then **16**, −10°C, 2.5 h; (b) DIBAH, toluene, −78°C, 2.5 h; (c) CBr_4, PPh_3, CH_2Cl_2, 0°C, 1 h; (d) **57**: **56**, PPh_3, CH_3CN, 70°C, 4.5 h; (e) **58**: (i) **55**, *n*-BuLi, THF, 0°C, 10 min, then TsCl, 0°C, 3 h; (ii) $HPPh_2$, *n*-BuLi, THF, 0°C, 6 h; (iii) H_2O_2, CH_2Cl_2/H_2O, 22°C, 2 h; (f) **59**: (i) 1-phenyl-5-mercapto-tetrazole, PPh_3, then **55**, *i*-$PrO_2CN{=}NCO_2i$-Pr, THF, 0°C, 1.5 h; (ii) H_2O_2/H_2O, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O_{cat.}$, EtOH, 22°C, 10 h; (g) **60**: (i) 2-mercaptobenzothiazole, PPh_3, then **55**, *i*-$PrO_2CN{=}NCO_2i$-Pr, THF, 0°C, 1.5 h; (ii) H_2O_2/H_2O, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O_{cat.}$, EtOH, 22°C, 17 h.

side chain with an appropriate activating group. To the best of our knowledge this coupling strategy remained unexplored in vitamin D chemistry presumably due to the lability of the A-ring ketone towards the elimination/aromatization anticipated or rapid enolization. On the other hand, this strategy benefits from the advantage of the C_2 symmetry of the diacetoxy ketone **30** generating an exocyclic double bond after olefination with no need for control of the geometry. Additionally, the configuration of the second *trans* double bond required in the side chain should also be more easily controllable than during the final assembly of the building blocks as for the previous strategy employed above.

For a thorough evaluation of the final assembly strategy we prepared the triphenyl phosphonium bromide **57**, the phosphinoxide **58**, the 2-phenyltetrazolyl sulfone **59** and the 2-benzothiazolyl sulfone **60** according to Scheme 7; the potential precursors to the Wittig, Horner or modified Julia coupling envisaged. An efficient and stereoselective synthesis to the C_2 elongated ester **54** was established by the Horner reaction of the aldehyde **16** with triethylphosphonoacetate affording a 97:3 mixture in favour of the desired *E*-isomer **54**, which was readily separable by chromatography on silica gel to provide the pure *E*-isomer **54** in 96% yield. DIBAH reduction of **54** furnished the allyl alcohol **55** (quant.), which was converted to the target molecules **57** (via **56**, 77% overall), **58** (64%), **59** (38%) and **60** (77%).

In the synthesis of the sulfone **59**, the allyl alcohol **61** (11%) was also formed, presumably by an initial [2,3]-sigmatropic rearrangement of the intermediate sulfoxide to the allyl sulfenate ester.[37] This side reaction was not observed in



Scheme 8. *Reagents and conditions:* (a) (i) **60**, $LiN(TMS)_2$, THF, −78°C, 35 min, then **30**, −78°C, 4 h and 22°C, 18 h; (ii) K_2CO_3, $MeOH/H_2O$, 22°C, 22 h.

the case of the sulfone **60** under identical conditions, attributable to the more electron withdrawing property of the 2-phenyltetrazolyl compared to the benzothiazolyl residue, accelerating the rearrangement.

A first olefination screening of activated methylene components **57** and **58** with the diacetoxy ketone **30** using *n*-BuLi at −78°C preferentially led to phenol as the major product resulting from aromatization of the base sensitive ketone **30**. With the sulfones **59** and **60**, however, we obtained for the first time the desired diene **62** (Scheme 8) albeit only in a low yield of 30–40%. For further optimization the more readily accessible 2-benzothiazolyl sulfone **60** was selected, which after deprotonation with $LiN(TMS)_2$ was smoothly converted to the still TES-protected and not isolated retiferol **62** readily transformed into the pure retiferol **3** in a high overall yield of 85% (from **30** and **60**) using K_2CO_3/$MeOH/H_2O$. These results indicate that the modified Julia olefination represents a highly efficient method compatible with the base sensitive ketone **30** presumably due to the lower basicity of the sulfone anion compared to the phosphorus ylides.

3. Summary

Novel practical approaches to both enantiomers of the phosphinoxides **6** and **40**, useful building blocks to access 19-*nor* vitamin D derivatives, were developed based on highly selective enzymatic desymmetrizations of the *meso*-1,3,5-trihydroxy cyclohexane derivatives **27** and **18**, respectively. These routes also provided efficient access to the enantiopure (*S*)- and (*R*)-5-acetoxy-2-cyclohexenone (**31**) and (**32**), previously unknown but highly potential building blocks for natural product synthesis applying stereoselective conjugate organo cuprate addition reactions. From a variety of assembly strategies evaluated, the uncommon **C**-disconnection, realised by application of a modified Julia olefination involving the ketone **30** and the sulfone **60**, emerged as the most efficient strategy completing a new short and high yielding route (Scheme 8) to the retiferol **3**.

4. Experimental

4.1. General

Mp: Tottoli or Büchi 535, uncorrected. Optical rotations: Perkin–Elmer Polarimeter 241. IR-spectra: Nicolet, FT-IR 20 SXB. ^{1}H NMR-spectra: Bruker AC 250 or AM 400, internal standard TMS, *J* values in Hz. MS-spectra: Finnigan MAT SSQ 7000, EI at 70 eV. GLC: Perkin Elmer AutoSystem and HP5890-II. HPLC: Agilent 1100. Monitoring of reactions by GLC with PS-088 capillary column (5% phenyl- 95% methyl-polysiloxane): **9**–**16**, **18**–**19**; OV-1-OH: **19**–**20**, **27/28**–**29**; remaining reactions monitored by TLC on silica gel (Merck) with *n*-hexane/AcOEt of various ratios. Chromatographic purifications on silica gel Si 60 (40–63 μm) from Merck.

4.2. Materials

GLC-columns BGB (β-cyclodextrin): BGB-Analytik AG, Laufenrainweg 139, CH-4469 Anwil; GLC-column Optima-240: Macherey Nagel AG, P.O. 224, CH-4702 Oensingen. HPLC-column Chiracel OD-H: Daicel or Merck. *Cis*-Triol **17**: Fluka; 1:1-mixture of **17/26**: Tokyo Kasei; Al_2O_3, basic, activity I: CAMAG; Lipases QL and OF: Meito Sangyo Co., Tokyo.

4.2.1. 8-*tert*-Butyloxy-4,4-dimethyl-octan-2-one (11). A tenth of a solution of 1-*tert*-butyloxy-4-chloro-butane (**9**) (67.84 g, 412 mmol) in THF (400 ml) was added dropwise to a suspension of magnesium powder (10.33 g, 425 mmol) in THF (20 ml). The reaction was started by the addition of a small amount of iodine, the remaining solution was added at reflux temperature over 40 min and stirring was continued at reflux temperature for 3.5 h. The black suspension was cooled to 22°C and added at −10°C to a suspension of CuI (8.58 g, 45 mmol) in THF (90 ml) over 40 min. The mixture was cooled to −20°C and treated with mesityl oxide (44.93 g, 90% pure, 412 mmol) over 15 min and stirring was continued at −20°C for 1 h. The reaction mixture was washed with aqueous NH_4Cl (15%, 600 ml) and with brine (600 ml), the organic layer was dried and the solvent evaporated to give the crude title compound **11** (84.49 g, 75.8% GLC purity, 68% yield) as a pale brown oil, which was further processed without purification. For analytical purposes a sample was purified over silica gel (hexane/AcOEt 10:1). IR (neat): 1718 s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 3.33 (t, *J*=6.5 Hz, 2H, OCH_2), 2.32 (s, 2H, $H_2C(3)$), 2.13 (s, 3H, CH_3CO), 1.49 and 1.30 (m each, 2H and 4H, 3×CH_2), 1.19 (s, 9H, $(CH_3)_3C$, 0.98 (s, 6H, $(CH_3)_2C$). MS: 213/3 $[M-CH_3]^+$, 171/10, 155/25, 97/95, 57/85, 43/100. $C_{16}H_{23}F_6O_2$ requires for $[M-CH_3]^+$: 361.1602; found for $[M-CH_3]^+$: 361.1592.

4.2.2. 10-*tert*-Butyloxy-1,1,1-trifluoro-6,6-dimethyl-2-trifluoromethyl-dec-3-yn-2-ol (12). To a solution of diisopropyl amine (27.62 g, 273 mmol) in THF (28 ml) was added at −78°C *n*-BuLi (1.6 M, 171 ml, 273 mmol), the solution was warmed to 0°C for 30 min and cooled to −78°C. To this solution was added a solution of the crude ketone **11** (59.38 g, 74.4% GLC purity, 193.5 mmol) in THF (20 ml) over 40 min and stirring was continued at −78°C for 1 h. The yellow solution was treated at −78°C with diethyl chlorophosphate (47.11 g, 262 mmol) over 30 min, the solution was allowed to warm to 22°C over 2 h and stirring was continued for 2 h. The pale yellow suspension containing the intermediate enol phosphate was added at −78°C to a solution of LDA, prepared from diisopropyl amine (52.62 g, 520 mmol) and *n*-BuLi (1.6 M, 325 ml, 520 mmol) in THF (60 ml) as described above, over 20 min and stirring was continued at −78°C for 2 h. The orange suspension was treated at −78°C with hexafluoro acetone (60.0 g, 97% purity, 351 mmol) and stirring was continued at −78°C for 30 min. The suspension was washed with sat. aqueous NH_4Cl (400 ml) and with brine (400 ml), the organic layer was dried and the solvent was evaporated. To remove traces of THF, the residue was dissolved in *n*-hexane (300 ml) and evaporated again. The residue was dissolved in *n*-hexane (300 ml), the solution cooled to 0°C and the suspension was stirred at 0°C for 1 h and at −20°C for 16 h. The suspension was filtered, the residue was washed with cold (−20°C) *n*-hexane (150 ml) and dried to give the pure title compound **12** (43.00 g, 59% yield) as white crystals, mp 66–67°C. The

mother liquor was purified over silica gel (hexane/AcOEt 19:1) to give a further portion of **12** (23.82 g, 33% yield) as white crystals, mp 60–64°C. IR (nujol): 3157 m (OH), 2242 m (C,C triple bond). ^{1}H NMR (250 MHz, $CDCl_3$): 4.6 (s, br., 1H, OH), 3.40 (t, J=6.5 Hz, 2H, OCH_2), 2.16 (s, 2H, $H_2C(5)$), 1.52 and 1.32 (m each, 2H and 4H, 3×CH_2), 1.20 (s, 9H, $(CH_3)_3C$), 0.97 (s, 6H, $(CH_3)_2C$). MS: 361/20 $[M-CH_3]^+$, 115/30, 57/100. $C_{13}H_{25}O_2$ requires for $[M-CH_3]^+$: 213.1855; found for $[M-CH_3]^+$: 213.1854.

4.2.3. (3*Z*)-10-*tert*-Butyloxy-1,1,1-trifluoro-6,6-dimethyl-2-trifluoromethyl-dec-3-en-2-ol (13). A suspension of alkyne **12** (20.00 g, 53.1 mmol) in *tert*-butyl methyl ether (200 ml) and Lindlar's catalyst ($Pd/CaCO_3/Pb$ (4.5%), 3.00 g) was hydrogenated at 22°C and 1 bar of hydrogen for 1.5 h after which time hydrogen up-take ceased. The suspension was filtered and the filtrate evaporated to dryness to give the pure title compound (3*Z*)-**13** (20.11 g, 100% yield) as a colourless oil, containing (3*E*)-**13** (1.4% GLC, Optima-240). IR (neat): 3260 m (OH), 1665w (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): 6.08 (td, J=8.1, 12.3 Hz, 1H, H–C(4)), 5.48 (d, br., J=12.3 Hz, 1H, H–C(3)), 3.40 (s, br., 1H, OH), 3.34 (t, J=6.5 Hz, 2H, OCH_2), 2.39 (d, br., J=8.1 Hz, 2H, $H_2C(5)$), 1.55–1.20 (m, 6H, 3×CH_2), 1.19 (s, 9H, $(CH_3)_3C$), 0.90 (s, 6H, $(CH_3)_2C$). MS: 363/5 $[M-CH_3]^+$, 115/30, 57/100. $C_{17}H_{28}F_6O_2$ requires: C 53.96%, H 7.46%, F 30.12%; found: C 54.12%, H 7.43%, F 30.25%.

4.2.4. (7*Z*)-10,10,10-Trifluoro-5,5-dimethyl-9-trifluoromethyl-dec-7-ene-1,9-diol (14). A mixture of the alkene **13** (20.11 g, 53.1 mmol) in *i*-PrOH (40 ml) and sulfuric acid (50%, 20.7 g) was heated to reflux temperature for 2 h and evaporated to dryness. The residue was dissolved in dichloromethane (100 ml) and washed with sat. $NaHCO_3$ (100 ml) and brine (100 ml), the organic layer was dried and the solvent evaporated to give the crude title compound **14** (16.44 g, 93.6% GLC purity, 90% yield) as a colourless oil, which was further processed without purification. IR (neat): 3253 m (OH), 1650 w (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): 6.08 (td, J=7.6, 12 Hz, 1H, H–C(7)), 5.49 (d, br., J=12 Hz, 1H, H–C(8)), 4.1 and 1.8 (s br. each, 2H, 2×OH), 3.66 (t, J=6 Hz, 2H, OCH_2), 2.40 (d, br., J=7.6 Hz, 2H, $H_2C(6)$), 1.55, 1.35 and 1.20 (m each, 2H each, 3×CH_2), 0.92 (s, 6H, $(CH_3)_2C$). MS: (neg. ion spray): 321/100 $[M-H]^-$. $C_{13}H_{20}F_6O_2$ requires: C 48.45%, H 6.26%, F 35.37%; found: C 48.41%, H 6.39%, F 35.34%.

4.2.5. (7*Z*)-10,10,10-Trifluoro-9-hydroxy-5,5-dimethyl-9-trifluoromethyl-dec-7-en-1-al (15). To a solution of the diol **14** (3.39 g, 95.9% GLC purity, 10.1 mmol) in dichloromethane (15 ml) was added a solution of KBr (90 mg) and $NaHCO_3$ (336 mg) in water (14 ml) followed by addition of TEMPO (8.5 mg, 0.054 mmol) and the mixture was treated at 0°C under vigorous stirring with NaOCl (10.8%, 8.00 g, 11.57 mmol) over 1 h. The aqueous layer was extracted twice with dichloromethane (15 ml each), the organic layers were washed with brine (15 ml), dried and the solvent evaporated to give the pure title compound **15** (2.92 g, 90% yield) as a pale yellow oil. IR (neat): 3360m (OH), 1718 s (C=O), 1665 w (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): 9.75 (s, br. 1H, CHO), 6.09 (td, J=8.0, 12.2 Hz, 1H, H–C(7)), 5.53 (d, br., J=12.2 Hz, 1H, H–C(8)), 3.80 (s, br., 1H, OH), 2.45, 1.60 and 1.20 (m each, 4H, 2H and 2H 4×CH_2), 0.93 (s, 6H, $(CH_3)_2C$). MS: 287/3 $[M-CH_3-H_2O]^+$, 231/10, 113/15, 95/100, 69/75. $C_{13}H_{18}F_6O_2$ requires: C 48.75%, H 5.67%, F 35.59%; found: C 48.95%, H 5.74%, F 35.43%.

4.2.6. (7*Z*)-10,10,10-Trifluoro-5,5-dimethyl-9-triethylsilanyloxy-9-trifluoromethyl-dec-7-en-1-al (16). To a solution of the aldehyde **15** (6.73 g, 85.2% GLC purity, 17.9 mmol) in THF (67 ml) was subsequently added at 22°C NEt_3 (2.55 g, 25.2 mmol), 4-dimethylamino pyridine (128 mg, 1.05 mmol) and triethylsilyl chloride (3.92 g, 97% pure, 25.2 mmol) and stirring was continued at 22°C for 1.5 h. The suspension was evaporated, the residue dissolved in dichloromethane (90 ml) and washed with hydrochloric acid (0.1N, 90 ml) and brine (90 ml). The organic layer was dried, the solvent evaporated and the residue purified over silica gel (hexane/AcOEt 9:1) to give the title compound **16** (7.50 g, 94.5% GLC purity, 91% yield) as a colourless oil. IR (neat): 1729 s (C=O), 1661 w (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): 9.77 (t, J=1.7 Hz, 1H, CHO), 5.97 (td, J=7.3, 12.4 Hz, 1H, H–C(7)), 5.45 (d, br., J=12.4 Hz, 1H, H–C(8)), 2.38, 1.60 and 1.20 (m each, 4H, 2H and 2H, 4×CH_2), 0.96 and 0.73 (t and q, J=8.2 Hz each, 9H and 6H, $Si(CH_2CH_3)_3$), 0.91 (s, 6H, $(CH_3)_2C$). MS: 405/10 $[M-C_2H_5]^+$, 95/100, 69/7. $C_{19}H_{32}F_6O_2Si$ requires: C 52.52%, H 7.42%, F 26.23%; found: C 52.39%, H 7.46%, F 26.17%.

4.2.7. *cis*-5-(*tert*-Butyldimethylsilanyloxy)-cyclohexane-1,3-diol (18). To a suspension of the *cis*-triol **17** (74.01 g, 560.0 mmol) in THF (1480 ml) was added subsequently at 22°C *tert*-butyldimethylsilyl chloride (95.72 g, 97% pure, 616 mmol) and NEt_3 (62.33 g, 616 mmol) and the suspension was treated in one portion with NaH (24.64 g, 60% in oil, 616 mmol) whereby the temperature rose slowly to 45°C over 30 min. After 2 h at 40°C the suspension was cooled to 10°C and filtered. The filtrate was evaporated and the residue triturated at 22°C with *n*-hexane (750 ml). Filtration of the suspension and drying of the residue afforded the pure title compound **18** (128.0 g, 93% yield) as a white solid, mp 121–122°C. IR (nujol): 3418 m, 3337 m and 3256 m (OH). ^{1}H NMR (250 MHz, $CDCl_3$): 3.78 (m, 3H, 3×H–CO), 2.28–1.93 and 1.55 (m each, 5H and 3H, 3×CH_2 and 2×OH), 0.89 (s, 9H, $(CH_3)_3C$), 0.08 (s, 6H, $(CH_3)_2Si$). MS: 189/2 $[M-C(CH_3)_3]^+$, 171/45, 129/30, 119/28, 75/100. $C_{12}H_{26}O_3Si$ requires: C 58.49%, H 10.64%; found: C 58.53%, H 10.51%.

4.2.8. (1*R*,3*S*,5*S*)-1-Acetoxy-3-hydroxy-5-(*tert*-butyldimethylsilanyloxy)-cyclohexane (19). To a solution of the diol **18** (8.95 g, 36.3 mmol) in vinyl acetate (90 ml) and ethyl acetate (810 ml) was added at 22°C Lipase QL (895 mg) and stirring was continued at 22°C for 46 h. The reaction mixture was filtered, the filtrate concentrated and the residue dried at 0.01 mbar overnight to give the pure title compound **19** (10.55 g, 98.5% GLC purity, 99% yield) as a pale yellow oil. ee=>99% (GLC, BGB-172). $[\alpha]_D$=+4.98° ($CHCl_3$, 1%). IR (neat): 3431 m (OH), 1738s (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): 4.76 (m, 1H, H–C(1)), 3.73 (m, 2H, H–C(3) and H–C(5)), 2.22–2.03 and 1.54–1.37 (m each, 4H and 3H, 3×CH_2 and OH), 2.04 (s, 3H, $COCH_3$), 0.88 (s, 9H, $(CH_3)_3C$), 0.07 and 0.06 (s each, 3H each,

$(CH_3)_2Si$). MS: 289/1 $[M+H]^+$, 171/100, 129/33, 117/55, 79/45, 75/60, 43/47. $C_{14}H_{28}O_4Si$ requires: C 58.29%, H 9.78%; found: C 57.93%, H 9.48%.

4.2.9. (1*R*,3*R*,5*R*)-1-Acetoxy-3-*tert*-butylcarbonyloxy-5-(*tert*-butyldimethylsilanyloxy)-cyclohexane (20). A solution of the alcohol **19** (10.67 g, 98.5% GLC purity, 36.4 mmol) and triphenylphosphine (14.55 g, 55.5 mmol) in THF (107 ml) was cooled to 0°C and treated with a solution of diisopropyl azodicarboxylate (11.81 g, 95% purity, 55.5 mmol) and pivalic acid (5.67 g, 55.5 mmol) in THF (85 ml) over 1 h and stirring was continued at 0°C for 1 h. The yellow solution was evaporated, the residue triturated with *n*-hexane/AcOEt (9:1, 130 ml), the suspension was filtered and the filtrate evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt, 19:1) to give the pure title compound **20** (12.63 g, 93% yield) as a colourless oil. $[\alpha]_D=+11.77°$ ($CHCl_3$, 1%). IR (neat): 1733s (C═O). ^1H NMR (250 MHz, $CDCl_3$): 5.24 and 4.99 (m each, 1H each, H–C(1) and H–C(3)), 3.97 (m, 1H, H–C(5)), 2.30–1.85 and 1.60–1.35 (m each, 3H each, 3×CH_2), 2.03 (s, 3H, CH_3CO), 1.20 (s, 9H, $(CH_3)_3C$), 0.88 (s, 9H, $(CH_3)_3CSi$), 0.05 (s, 6H, $(CH_3)_2Si$). MS: 371/1 $[M-H]^+$, 315/10, 159/45, 117/100. $C_{19}H_{36}O_5Si$ requires: C 61.25%, H 9.74%; found: C 61.26%, H 9.70%.

4.2.10. (1*R*,3*R*,5*R*)-1-Hydroxy-3-*tert*-butylcarbonyloxy-5-(*tert*-butyldimethylsilanyloxy)-cyclohexane (21). To a solution of the pivaloate **20** (7.45 g, 20.0 mmol) in MeOH (52 ml) was added at 22°C a solution of K_2CO_3 (2.76 g, 20.0 mmol) in water (23.5 ml) and stirring was continued at 22°C for 7 h. The pale yellow solution was evaporated and the residue partitioned between dichloromethane (50 ml) and water (50 ml). The organic layer was dried and evaporated to give the pure title compound **21** (6.49 g, 98% yield) as a colourless oil, which solidified at 22°C, mp 41–42.5°C. IR (nujol): 3240 m, br. (OH),1731s (C═O). ^1H NMR (250 MHz, $CDCl_3$): 5.31 (m, 1H, H–C(3), 4.18 and 4.06 (m each, 1H each, H–C(1) and H–C(5)), 2.97 (d, br. J=6.4 Hz, 1H, OH), 1.94–1.64 (m, 6H, 3×CH_2), 1.19 (s, 9H, $(CH_3)_3C$), 0.91 (s, 9H, $(CH_3)_3CSi$), 0.11 and 0.09 (s each, 3H each, $(CH_3)_2Si$). MS: 273/10 $[M-C(CH_3)_3]^+$, 171/100, 159/35, 79/45, 75/90. $C_{17}H_{34}O_4Si$ requires: C 61.77%, H 10.37%; found: C 61.90%, H 10.62%.

4.2.11. (3*S*,5*S*)-3-*tert*-Butylcarbonyloxy-5-(*tert*-butyldimethylsilanyloxy)-cyclohexan-1-one (22). To a solution of the alcohol **21** (27.50 g, 83.2 mmol) in dichloromethane (250 ml) was added a solution of KBr (0.71 g) and $NaHCO_3$ (2.66 g) in water (250 ml) followed by addition of TEMPO (200 mg, 1.25 mmol) and the mixture was treated at 0°C under vigorous stirring with NaOCl (11%, 61.93 g, 91.52 mmol) over 1 h. The aqueous layer was extracted once with dichloromethane (250 ml), the organic layers were washed with aqueous NH_4Cl (15%, 250 ml) and brine (250 ml), dried and the solvent evaporated to give the pure title compound **22** (27.24 g, 100% yield) as a yellow oil. $[\alpha]_D=-20.37°$ ($CHCl_3$, 1%). IR (neat): 1728 s, br. (C═O). ^1H NMR (250 MHz, $CDCl_3$): 5.37 (m, 1H, H–C(3), 4.30 (m, 1H, H–C(5)), 2.63, 2.43 and 2.06 (m each, 2H each, 3×CH_2), 1.18 (s, 9H, $(CH_3)_3C$), 0.97 (s, 9H, $(CH_3)_3CSi$), 0.08 and 0.07 (s each, 3H each, $(CH_3)_2Si$). MS: 271/3 $[M-C(CH_3)_3]^+$, 227/15, 169/30, 159/20, 57/100. $C_{17}H_{32}O_4Si$ requires: C 62.15%, H 9.82%; found: C 62.52%, H 9.81%.

4.2.12. (1*R*,3*R*)-1,3-Diacetoxy-5-(*tert*-butyldimethylsilanyloxy)-cyclohexane (23). A solution of the alcohol **19** (40.38 g, 98.5% GLC purity, 137.9 mmol) and triphenylphosphine (55.08 g, 210.0 mmol) in THF (400 ml) was cooled to 0°C and treated with a solution of diisopropyl azodicarboxylate (44.69 g, 95% purity, 210.0 mmol) and acetic acid (12.61 g, 210.0 mmol) in THF (220 ml) over 2 h and stirring was continued at 0°C for 2 h. The yellow solution was evaporated, the residue triturated with *n*-hexane/AcOEt (4:1, 300 ml), the suspension was filtered and the filtrate evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt, 9:1) to give the pure title compound **23** (42.26 g, 93% yield) as a colourless oil. $[\alpha]_D=+14.63°$ ($CHCl_3$, 1%). IR (neat): 1740s (C═O). ^1H NMR (250 MHz, $CDCl_3$): 5.27 and 5.02 (m each, 1H each, H–C(1) and H–C(3)), 3.97 (m, 1H, H–C(5)), 2.25–1.85 and 1.61–1.36 (m each, 3H each, 3×CH_2), 2.05 and 2.03 (s each, 3H each, 2×CH_3CO), 0.87 (s, 9H, $(CH_3)_3CSi$), 0.06 (s, 6H, $(CH_3)_2Si$). MS: 273/5 $[M-C(CH_3)_3]^+$, 213/5, 171/10, 117/100. $C_{16}H_{30}O_5Si$ requires: C 58.15%, H 9.15%; found: C 58.09%, H 9.12%.

4.2.13. (1*S*,3*S*)-1,3-Diacetoxy-5-hydroxy-cyclohexane (24). To a solution of the diacetate **23** (34.70 g, 105.0 mmol) in THF (350 ml) was added at 0°C tetrabutylammonium fluoride (1 M in THF, 115.5 ml, 115.5 mmol) over 30 min and stirring was continued at 0°C for 3 h. The solution was evaporated and the residue purified over silica gel (*n*-hexane/AcOEt, 1:2) to give the title compound **24** (20.05 g, 97.9% GLC purity, 87% yield), as a pale yellow oil. ee=87.2% (GLC, BGB-174). IR (neat): 3451 m, br. (OH), 1734s (C═O). ^1H NMR (250 MHz, $CDCl_3$): 5.29 and 5.05 (m each, 1H each, H–C(1) and H–C(3)), 4.04 (m, 1H, H–C(5)), 2.31–2.05 and 1.65–1.43 (m each, 3H each, 3×CH_2), 2.05 and 2.04 (s each, 3H each, 2×CH_3CO), 1.85 (s, br., 1H, OH). MS: 156/2 $[M-AcOH]^+$, 96/75, 43/100. $C_{10}H_{16}O_5$ (containing 0.81% of H_2O) requires: C 55.55%, H 7.46%; found: C 55.59%, H 7.43%.

4.2.14. (3*R*,5*R*)-3,5-Diacetoxy-cyclohexan-1-one (25). To a solution of the alcohol **24** (30.0 g, 97.9% GLC purity, 135.8 mmol) in dichloromethane (400 ml) was added a solution of KBr (1.16 g) in water (200 ml) followed by addition of TEMPO (325 mg, 2.1 mmol) and the mixture was treated at 0°C under vigorous stirring simultaneously with NaOCl (10.6%, 107.1 g, 152.6 mmol) and with hydrochloric acid (0.1N, 520 ml) over 1 h keeping the pH at 6.5–7.5. The aqueous layer was extracted once with dichloromethane (200 ml), the organic layers were washed with brine (300 ml), dried and the solvent evaporated to give the pure title compound **25** (28.93 g, 99% yield) as a pale yellow oil. ee=87% (GLC, BGB-174). A sample was crystallized from *tert*-butyl methyl ether/*n*-hexane at −20°C to give white crystals, mp 51–52°C. ee=99.0% (GLC, BGB-174). $[\alpha]_D=+56.5°$ ($CHCl_3$, 1%). IR (nujol): 1728s (C═O). ^1H NMR (400 MHz, $CDCl_3$): 5.37 (m, 2H, H–C(3) and H–C(5)), 2.73 and 2.52 (dd each, J=14.6+4, 14.6+6.8 Hz, 2H each, $H_2C(2)$ and $H_2C(6)$), 2.19 (t, J=5.6 Hz, 2H, $H_2C(4)$), 2.05 (s, 6H, 2×CH_3CO). MS: 154/5 $[M-AcOH]^+$, 112/20, 94/25,

43/100. $C_{10}H_{14}O_5$ requires: C 56.07%, H 6.59%; found: C 55.93%, H 6.76%.

4.2.15. 77:18 Mixture of *trans*-1,3,5-triacetoxy-cyclohexane (27) and *cis*-1,3,5-triacetoxy-cyclohexane (28). A solution of a 1:1 mixture of the *trans*-triol **26** and the *cis*-triol **17** (87.34 g) in ethanol (870 ml) was diluted at 22°C with water (38 ml) and cooled to 0°C. The solution was seeded with pure **17** and stirring was continued at 0°C for 1 h and at −20°C for 4 h. The suspension was filtered, the filtrate evaporated, the residue was suspended in toluene (440 ml) and evaporated again to give a water free 76:18 mixture of the *trans*-triol **26** and the *cis*-triol **17** (44.00 g, 333.0 mmol) as a white solid. This mixture was treated at 22°C with pyridine (110 ml) and with acetic anhydride (157 ml, 1665 mmol) over 45 min after which time the temperature rose to 45°C and stirring was continued at 45°C for 4 h. The mixture was evaporated to dryness, the residue dissolved in dichloromethane (300 ml) and washed with hydrochloric acid (0.2N, 300 ml) and water (200 ml). The organic layer was dried and evaporated to give a 77:18 mixture (GLC) of the title compounds **27** and **28** (85.73 g, 100% yield) as a pale yellow oil. IR (neat): 1736s br. (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 5.31, 5.09 and 4.78 (m each, 3×H–CO of *trans*-**27** and *cis*-**28**), 2.07 and 2.04 (s each, 3×CH_3), 2.35–2.07 and 1.65–1.35 (m each, 3×CH_2). MS: 199/7 $[M-AcO]^+$, 138/20, 96/90, 78/35, 43/100. $C_{12}H_{18}O_6$ requires: C 55.81%, H 7.03%; found: C 55.94%, H 7.10%.

4.2.16. (1*R*,3*R*)-1,3-Diacetoxy-5-hydroxy-cyclohexane (29). To a 77:18 mixture of the crude triacetates **27** and **28** (81.74 g, 243.7 mmol **27**) in cyclohexane (200 ml) was added under vigorous stirring a solution of sodium chloride (0.1 M, 1300 ml) and sodium phosphate buffer (0.1 M, pH=7.0, 50 ml). The resulting mixture was cooled to 5–6°C and the pH re-adjusted to 7.0 with aqueous sodium hydroxide (1N, few drops). The reaction was started by adding a solution of Lipase OF (1.60 g) in aqueous sodium chloride (0.1 M, 15 ml) to the vigorously stirred mixture and the pH was kept constant at 7.0 by the controlled addition (pH-stat) of aqueous sodium hydroxide (1N, 260 ml, 1.07 equiv. with respect to **27**) over 21.5 h keeping the temperature at 5–6°C. The reaction mixture was extracted twice with dichloromethane (1500 ml each), the organic, very turbid layers were filtered over Dicalite Speedex (100 g, prewashed with water) dried and evaporated. The residue (66.1 g) was purified over silica gel (700 g, *n*-hexane/ethyl acetate 3:2) to give the title compound **29** (46.3 g 95.7% GLC purity, 84% yield with respect to **27**) as a colourless oil. ee=99.5% (GLC, BGB-174). IR, ^{1}H NMR and MS are identical with the enantiomer **24**. $C_{10}H_{16}O_5$ requires: C 55.55%, H 7.46%; found: C 55.76%, H 7.37%.

4.2.17. (3*S*,5*S*)-3,5-Diacetoxy-cyclohexan-1-one (30). The oxidation was carried out with the alcohol **29** according to the preparation of the enantiomer **25** to give the pure title compound **30** (99% yield) as a pale yellow oil which solidified at −20°C. For analytical purposes a sample was recrystallized from *tert*-butyl methyl ether/*n*-hexane at −20°C to give white crystals, mp 51–52°C. ee=99.5% (GLC, BGB-174). $[\alpha]_D=-56.1°$ ($CHCl_3$, 1%). IR, ^{1}H NMR and MS are identical with **25**. $C_{10}H_{14}O_5$ requires: C 56.07%, H 6.59%; found: C 55.98%, H 6.65%.

4.2.18. (5*S*)-5-Acetoxy-cyclohex-2-en-1-one (31). A suspension of the ketone **30** (5.00 g, 23.35 mmol) in THF (50 ml) and aluminium oxide (basic, activity I, 25.0 g) was stirred at 22°C for 1 h and the reaction was followed by ^{1}H NMR. The suspension was filtered, the filtrate evaporated and the residue triturated with *tert*-butyl methyl ether (4 ml) at 22°C for 1 h. The suspension was filtered and the residue dried to give the pure title compound **31** (2.75 g, 76% yield) as white crystals, mp 84–86°C. The mother liquor was evaporated and subsequently triturated with *n*-pentane (1.5 ml) and with *tert*-butyl methyl ether (2 ml) at 22°C to give a further portion of pure **31** (0.28 g, 8% yield). ee=>99.9% (GLC, BGB-176). $[\alpha]_D=+43.6°$ ($CHCl_3$, 1%). IR (nujol): 1731s and 1671s (C=O), 1625 m (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 6.88 (td, J=4, 10.2 Hz, 1H, H–C(3)), 6.12 (td, J=1.6, 10.2 Hz, 1H, H–C(2)), 5.35 (m, 1H, H–C(5)), 2.80–2.48 (m, 4H, 2×CH_2), 2.05 (s, 3H, CH_3CO). MS: 154/3 $[M]^+$, 111/10, 94/37, 68/40, 43/100. $C_8H_{10}O_3$ requires: C 62.33%, H 6.54%; found: C 62.12%, H 6.57%.

4.2.19. (5*R*)-5-Acetoxy-cyclohex-2-en-1-one (32). The elimination was carried out with the ketone **25** (ee=87%) according to the preparation of the enantiomer **31** to give the pure title compound **32** (70% yield) as white crystals, mp 84–86°C. ee=98.8% (GLC, BGB-176). $[\alpha]_D=-43.0°$ ($CHCl_3$, 1%). IR, ^{1}H NMR and MS are identical with **31**. $C_8H_{10}O_3$ requires: C 62.33%, H 6.54%; found: C 62.05%, H 6.64%.

4.2.20. Ethyl ((3*R*,5*R*)-3,5-diacetoxy-cyclohexylidene)-acetate (34). To a solution of LDA (0.2 M in THF, 1000 ml, 200 mmol) was added at −78°C a solution of ethyl (trimethylsilyl)–acetate (33.05 g, 97% pure, 200.0 mmol) in THF (100 ml) over 1 h followed by addition of a solution of the ketone **30** (21.42 g, 100.0 mmol) in THF (150 ml) and stirring was continued at −78°C for 1.5 h. The yellow solution was washed with aqueous sat. NH_4Cl (500 ml) and brine (500 ml), the organic layer was dried and evaporated. Purification of the residue over silica gel (hexane/AcOEt 4:1) gave the pure title compound **34** (23.57 g, 83% yield) as a pale yellow. IR (neat): 1734 s and 1712 s (C=O), 1656m (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 5.78 (s, br., 1H, HC=C), 5.20 and 5.14 (m each, 1H each, H–C(3) and H–C(5)), 4.16 (q, J=7.2 Hz, 2H, $COOCH_2$), 3.07, 2.56, 2.33 and 2.00 (m, dd, dd, and m, J=13.4+4.4, 13.4+7.6 Hz, 2H, 1H, 1H and 2H, 3×CH_2), 2.05 and 2.02 (s each, 3H each, 2×CH_3CO), 1.28 (t, J=7.2 Hz, 3H, CH_3). MS: 284/1 $[M]^+$, 225/5 $[M-CH_3CO_2]^+$, 164/85, 136/80, 118/55, 91/60, 43/100. $C_{14}H_{20}O_6$ requires: C 59.15%, H 7.09%; found: C 58.88%, H 7.09%.

4.2.21. 3:1 Mixture of ethyl ((3*R*,5*R*)-3,5-dihydroxy-cyclohexylidene)-acetate (35) and its methyl acetate. To a solution of the ethyl ester **34** (21.60 g, 75.97 mmol) in methanol (160 ml) was added at 0°C a solution of K_2CO_3 (21.0 g, 152 mmol) in water (74 ml) and the solution was stirred vigorously at 22°C for 6 h. The mixture was evaporated, the residue partitioned between dichloromethane (300 ml) and brine (300 ml) and the aqueous layer was extracted four times with dichloromethane (300 ml each). The combined organic layers were dried and evaporated to

give a 3:1 mixture (^{1}H NMR) of the title compound **35** and its methyl acetate (14.75 g, 99% yield) as a yellow oil. IR (neat): 3392s, br. (OH), 1712s (C=O), 1651s (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 5.82 (s, br., HC=C), 4.30–4.17 (m, H–C(3) and H–C(5)), 4.15 (q, J=6.8 Hz, $COOCH_2$), 3.70 (s, $COOCH_3$), 3.12, 2.88, 2.55 and 2.25–1.75 (m each, 3×CH_2 and 2×OH), 1.28 (t, J=6.8 Hz, CH_3 of ethyl acetate). MS: 200/5 $[M]^+$ of **35**, 182/20 $[M-H_2O]^+$ of **35**, 155/80, 82/100. $C_{10}H_{16}O_4$ requires: 200.1049; found: 200.1039.

4.2.22. 3:1 Mixture of ethyl [(3*R*,5*R*)-3,5-bis-(*tert*-butyldimethylsilanyloxy)-cyclohexylidene]-acetate (36) and its methyl acetate. To a solution of a 3:1 mixture of the ethyl acetate **35** and its methyl acetate (13.80 g, 70.14 mmol) in DMF (70 ml) was added in one portion at 22°C *tert*-butyldimethylsilyl chloride (23.56 g, 97% pure 151.6 mmol) and in five portions imidazole (10.32 g, 151.6 mmol) and stirring of the suspension was continued at 22°C for 3 h. The mixture was diluted at 10°C with toluene (150 ml) and water (150 ml), the organic layer was washed several times with water, dried and evaporated to give a 3:1 mixture (^{1}H NMR) of the title compound **36** and its methyl acetate (29.05 g, 97% yield) as a pale yellow oil. For analytical purposes a sample was purified over silica gel (*n*-hexane/AcOEt 50:1). IR (neat): 1721s (C=O), 1655 m (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): 5.70 (s, br., HC=C), 4.20–4.10 (m, H–C(3) and H–C(5)), 4.15 (q, J=7 Hz, $COOCH_2$), 3.68 (s, $COOCH_3$), 3.03, 2.80, 2.38, 2.16, 1.80 and 1.70 (m each, 3×CH_2), 1.27 (t, J=7 Hz, CH_3 of ethyl acetate), 0.87 and 0.85 (s each, 2×$(CH_3)_3C$), 0.05 (s, 2×$(CH_3)_2Si$). MS: 371/100 $[M-C(CH_3)_3]^+$ of **36**, 357/40 $[M-C(CH_3)_3]^+$ of methyl acetate, 73/55. $C_{22}H_{44}O_4Si_2+C_{21}H_{42}O_4Si_2$ (3:1) requires: C 61.43%, H 10.31%; found: C 61.41%, H 10.43%.

4.2.23. [(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-cyclohexylidene]-ethanol (37). To a solution of a 3:1 mixture of the ethyl acetate **36** and its methyl acetate (27.00 g, 63.5 mmol) in toluene (270 ml) was added at −15°C Red-Al® (3.5 M in toluene, 43 ml, 150.5 mmol) over 30 min and stirring was continued at −15°C for 1 h. The yellow solution was slowly diluted at −15 to 0°C with water (140 ml) and the emulsion was further diluted with aqueous NaOH (1N, 135 ml). The organic layer was washed several times with water, dried and evaporated to give the title compound **37** (23.36 g, 95% yield) as a colourless wax, which was further processed without purification. For analytical purposes a sample was purified over silica gel (*n*-hexane/AcOEt 7:1), mp 63–65°C. $[\alpha]_D$=+18.4° ($CHCl_3$, 1%). Prepared according to lit.:[9] $[\alpha]_D$=+18.7° ($CHCl_3$, 1%). IR (nujol): 3240s, br. (OH), 1675w (C=C); MS (EI): 371/3 $(M-CH_3)$. ^{1}H NMR (400 MHz, $CDCl_3$): 5.60 (t, J=7.3 Hz, 1H, HC=C), 4.13 and 4.03 (m each, 2H each, H–C(3), H–C(5) and CH_2O), 2.35, 2.18, 2.06, 1.82, 1.64 and 1.30 (m, dd, dd, m, m and t, J=13+2.4, 13+8.1, 6.5 Hz Hz, 2H, 1H, 1H, 1H, 1H and 1H, 3×CH_2 and OH), 0.89 (s, br., 18H, 2×$(CH_3)_3C$), 0.06, 0.05 and 0.04 (s each, 6H, 3H and 3H, 2×$(CH_3)_2Si$). MS: 371/3 $[M-CH_3]^+$, 237/45, 211/40, 197/50, 171/100, 75/90. IR, ^{1}H NMR and MS are identical with **37** prepared according to lit.[9]. $C_{20}H_{42}O_3Si_2$ requires: C 62.12%, H 10.95%; found: C 62.23%, H 11.03%.

4.2.24. [(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-cyclohexylidene]-ethyl-diphenylphosphine oxide (6). To a solution of the allyl alcohol **37** (9.67 g, 25.0 mmol) in THF (97 ml) was subsequently added at 0°C *n*-BuLi (1.6 M in hexane, 16.4 ml, 26.2 mmol) over 20 min and a solution of toluene-4-sulfonyl chloride (5.00 g, 26.2 mmol) in THF (50 ml) over 30 min and stirring was continued at 0°C for 2.5 h. The pale yellow solution was treated at 0°C over 1 h with a solution of lithium diphenylphosphide, prepared by addition of *n*-BuLi (1.6 M in hexane, 17.2 ml, 27.5 mmol) to a solution of diphenylphosphine (5.12 g, 27.5 mmol) in THF (40 ml) over 1 h, and the orange solution was stirred at 0°C for 1 h. The mixture was slowly diluted with 5 ml of water and evaporated. The residue was diluted with dichloromethane (200 ml) and water (200 ml) and the vigorously stirred mixture was treated at 22°C with hydrogen peroxide (35%, 24.3 g, 250 mmol) and stirring was continued for 3.5 h. The organic layer was washed with aqueous sat. $NaHCO_3$ (300 ml) and water (300 ml), dried and evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt 2: 1) to give the pure title compound **6** (10.71 g, 75% yield) as a white solid. For analytical purposes a sample was recrystallized from *n*-hexane at −50°C, mp 73–75°C. ee=>99.9% (HPLC, Chiracel OD–H, *n*-hexane/EtOH 9:1). $[\alpha]_D$=+13.8° ($CHCl_3$, 1%). IR (KBr): 1180s (P=O). ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 and 7.47 (m each, 4H and 6H, H-ar.), 5.28 (q, J=7.2 Hz, 1H, HC=C), 3.98 (m, 2H, H–C(3) and H–C(5)), 3.10 (m, 2H, CH_2P), 2.21, 2.00, 1.90 and 1.64 (m each, 1H, 2H, 1H and 2H, 3×CH_2), 0.85 and 0.83 (s each, 9H each, 2×$(CH_3)_3C$), 0.00 and −0.01 (s each, 12H, 2×$(CH_3)_2Si$). MS: 555/3 $[M-CH_3]^+$, 513/100 $[M-C(CH_3)_3)]^+$, 381/80, 202/75, 73/87. IR, ^{1}H NMR and MS are identical with **6** prepared according to lit.[9]. $C_{32}H_{51}O_3PSi_2$ requires: C 67.32%, H 9.00%, P 5.43%; found: C 67.22%, H 8.96, P 5.32%.

4.2.25. [(3*S*,5*S*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-cyclohexylidene]-ethyl-diphenylphosphine oxide (40). The preparation of the enantiomer **40** from the ketone **25** (ee=86%) was carried out in analogy to **6** to give the title compound **40**, which was recrystallized from *n*-hexane at −50°C, mp 73–75°C. ee=>99.9% (HPLC, Chiracel OD–H, *n*-hexane/EtOH 9:1). $[\alpha]_D$=−13.4° ($CHCl_3$, 1%). IR, ^{1}H NMR and MS are identical with **6**. $C_{32}H_{51}O_3PSi_2$ requires: C 67.32%, H 9.00%, P 5.43%; found: C 67.11%, H 9.00, P 5.55%.

4.2.26. (2*E*,9*Z*)-12,12,12-Trifluoro-7,7-dimethyl-11-triethylsilanyloxy-11-trifluoromethyl-dodeca-2,9-dienoic acid ethyl ester (54). To a suspension of *tert*-BuOK (16.83 g, 150 mmol) in toluene (450 ml) was added at 5°C a solution of triethyl phosphonoacetate (33.60 g, 150 mmol) in toluene (120 ml) over 30 min and stirring was continued at 22°C for 1 h. The suspension was cooled to −15°C and treated with a solution of the aldehyde **16** (50.00 g, 95.4% GLC purity, 109.8 mmol) in toluene (120 ml) over 30 min and stirring was continued at −10°C for 2.5 h. The reaction mixture was quenched with aqueous NH_4Cl (15%, 500 ml), the organic layer was washed twice with water (500 ml each), dried and evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt 40:1) to give a minor fraction containing the pure (2*Z*,9*Z*)-isomer of **54** (1.38 g, 2.5% yield). IR

(neat): 1723s (C═O), 1645m (C═C). ^{1}H NMR (400 MHz, $CDCl_3$): 6.19 (td, J=7.6, 11.4 Hz, 1H, H–C(3)), 5.96 (td, J=7.0, 12.4 Hz, 1H, H–C(9)), 5.76 (td, J=1, 11.4 Hz, 1H, H–C(2)), 5.43 (d, br., J=12.4 Hz, 1H, H–C(10)), 4.17 (q, J=6.8 Hz, 2H, CH_2O), 2.62 (qd, J=7.6, 1.6 Hz, 2H, $H_2C(4)$), 2.32 (dd, J=7, 2 Hz, 2H, $H_2C(8)$), 1.39 and 1.25 (m each, 2H each, 2×CH_2), 1.30 (t, J=6.8 Hz, 3H, CH_3), 0.96 and 0.72 (t and q, J=8 Hz each, 9H and 6H, $Si(CH_2CH_3)_3$), 0.88 (s, 6H, $(CH_3)_2C(7)$). MS: 505/1 $[M+H]^+$, 475/20 $[M-C_2H_5)]^+$, 325/10, 183/15, 137/40, 109/100. $C_{21}H_{33}F_6O_3Si$ requires for $[M-C_2H_5)]^+$: 475.2103; found for $[M-C_2H_5)]^+$: 475.2090.

The main fraction contained the pure title compound **54** (53.15 g, 96% yield) as a colourless oil. IR (neat): 1724s (C═O), 1655m (C═C). ^{1}H NMR (400 MHz, $CDCl_3$): 6.95 (td, J=7.0, 15.6 Hz, 1H, H–C(3)), 5.95 (td, J=7.0, 12.4 Hz, 1H, H–C(9)), 5.81 (d, br., J=15.6 Hz, 1H, H–C(2)), 5.43 (d, br., J=12.4 Hz, 1H, H–C(10)), 4.18 (q, J=6.8 Hz, 2H, CH_2O), 2.32 and 2.17 (d and q, J=7.0 Hz each, 2H and 2H, 2×CH_2), 1.42 and 1.25 (m each, 2H each, 2×CH_2), 1.28 (t, J=6.8 Hz, 3H, CH_3), 0.97 and 0.72 (t and q, J=7.6 Hz each, 9H and 6H, $Si(CH_2CH_3)_3$), 0.89 (s, 6H, $(CH_3)_2C(7)$). MS: 505/1 $[M+H]^+$, 475/15 $[M-C_2H_5)]^+$, 325/10, 183/5, 137/10, 109/100. $C_{21}H_{33}F_6O_3Si$ requires for $[M-C_2H_5)]^+$: 475.2103; found for $[M-C_2H_5)]^+$: 475.2088.

4.2.27. (2*E*,9*Z*)-12,12,12-Trifluoro-7,7-dimethyl-11-triethylsilanyloxy-11-trifluoromethyl-dodeca-2,9-dien-1-ol (55). To a solution of the ester **54** (53.10 g, 105.2 mmol) in toluene (650 ml) was added at −78°C diisobutyl aluminium hydride (1.2 M in toluene, 240 ml, 288 mmol) over 40 min and stirring of the colourless mixture was continued at −78°C for 2.5 h. The reaction was quenched with aqueous NH_4Cl (15%, 500 ml), the suspension was filtered and the aqueous layer extracted once with toluene (500 ml). The organic layers were washed twice with water (500 ml each), dried and evaporated to give the title compound **55** (48.52 g, 100%) as a pale yellow oil, which was further processed without purification. For analytical purposes a sample was purified over silica gel (*n*-hexane/AcOEt 4:1). IR (neat): 3328m (OH), 1669w (C═C). ^{1}H NMR (400 MHz, $CDCl_3$): 5.97 (td, J=6.5, 12.4 Hz, 1H, H–C(9)), 5.66 (m, 2H, H–C(2) and H–C(3)), 5.43 (d, br., J=12.4 Hz, 1H, H–C(10)), 4.09 (t, J=5,2 Hz, 2H, $H_2C(1)$), 2.32 (d, J=6.5 Hz, 2H, $H_2C(8)$), 2.02 (q, J=6.5 Hz, 2H, $H_2C(4)$), 1.35 and 1.25 (m each, 2H and 3H, 2×CH_2 and OH), 0.96 and 0.73 (t and q, J=8 Hz each, 9H and 6H, $Si(CH_2CH_3)_3$), 0.88 (s, 6H, $(CH_3)_2C(7)$). MS: 433/4 $[M-C_2H_5)]^+$, 231/25, 123/85, 81/100. $C_{21}H_{36}F_6O_2Si$ requires: C 54.53%, H 7.84%, F 24.64%; found: C 54.76%, H 7.78%, F 24.84%.

4.2.28. (2*E*,9*Z*)-2-(12,12,12-Trifluoro-7,7-dimethyl-11-triethylsilanyloxy-11-trifluoromethyl-dodeca-2,9-diene-1-sulfonyl)-benzothiazole (60). To a suspension of 2-mercaptobenzothiazole (16.56 g, 99 mmol) in dichloromethane (165 ml) was subsequently added at 0°C in one portion triphenylphosphine (25.97 g, 99 mmol), a solution of the allyl alcohol **55** (30.53 g, 66 mmol) in dichloromethane (90 ml) over 20 min and diisopropyl azodicarboxylate (21.07 g, 95% pure, 99 mmol) over 30 min and stirring was continued at 0°C for 1.5 h. The mixture was evaporated to dryness, the residue dissolved in EtOH (425 ml) and treated at 0°C with a solution of ammonium heptamolybdate tetrahydrate (16.31 g, 13.2 mmol) in H_2O_2 (35%, 64.15 g, 660 mmol) over 15 min and stirring was continued at 22°C for 17 h. The mixture was treated with a solution of Na_2SO_3 (76 g) in water (760 ml), the ethanol was distilled off and the aqueous layer was extracted twice with dichloromethane (500 ml each). The organic layers were washed with water (500 ml), dried and evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt, 15:1) to give the title compound **60** (32.90 g, 77%) as a pale yellow oil. IR (neat): 1663w (C═C), 1335 1148s (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): 8.23, 8.00 and 7.61 (d, d and m, J=7.6 Hz each, 1H, 1H and 2H, H-ar), 5.88 (td, J=7, 12.4 Hz, 1H, H–C(9)), 5.72 and 5.49 (td each, J=7, 15.6 Hz each, 1H each, H–C(2) and H–C(3)), 5.40 (d, br., J=12.4 Hz, 1H, H–C(10)), 4.18 (d, J=7 Hz, 2H, $H_2C(1)$), 2.24 (d, J=7 Hz, 2H, $H_2C(8)$), 1.96 (q, J=7 Hz, 2H, $H_2C(4)$), 1.12 (m, 4H, 2×CH_2), 0.95 and 0.71 (t and q, J=8 Hz each, 9H and 6H, $Si(CH_2CH_3)_3$), 0.76 (s, 6H, $(CH_3)_2C(7)$). MS: 643/1 $[M]^+$, 614/50 $[M-C_2H_5)]^+$ 182/100. $C_{28}H_{39}F_6NO_3S_2Si$ requires: C 52.24%, H 6.11%, N 2.18%, S 9.96%, F 17.71%; found: C 52.39%, H 6.24%, N 2.20%, S 10.18%, F 17.58%.

4.2.29. (1*R*,3*R*)-5-[(2*E*,9*Z*)12,12,12-Trifluoro-11-hydroxy-7,7-dimethyl-11-trifluoromethyl-dodeca-2,9-dienylidene]-cyclohexane-1,3-diol (3). A solution of the sulfone **60** (21.89 g, 34.0 mmol) in THF (130 ml) was treated at −78°C with $LiN(TMS)_2$ (1.0 M in THF, 34 ml, 34.0 mmol) over 45 min and stirring of the orange solution was continued for 35 min. The solution was treated at −78° with a solution of the ketone **30** (7.28 g, 34.0 mmol) in THF (36 ml) over 20 min and stirring was continued at −78°C for 4 h and at 22°C for 18 h. The mixture was evaporated to dryness and the residue dissolved in MeOH (440 ml). To the orange solution was added at 22°C a solution of K_2CO_3 (14.1 g) in water (110 ml) and stirring was continued at 22°C for 22 h. The orange emulsion was evaporated to dryness and the residue partitioned between dichloromethane (200 ml) and water (100 ml). The aqueous layer was extracted twice with dichloromethane (200 ml each) and the organic layers were washed with brine (100 ml), dried and evaporated. The residue was purified over silica gel (*n*-hexane/AcOEt 1:4) to give the pure title compound **3** (12.81 g, 85%) as a pale yellow resin, which is sensitive to air. $[\alpha]_D$+8.34° ($CHCl_3$, 1%). IR (neat): 3348 m (OH), 1662 w (C═C). ^{1}H NMR (400 MHz, $CDCl_3$): 6.26 (dd, J=10.8, 15.2 Hz, 1H, H–C(2)), 6.05 (td, J=8, 12.4 Hz, 1H, H–C(9)), 5.98 (d, br., J=10.8 Hz, 1H, H–C(1)), 5.68 (td, J=6.8, 15.2 Hz, 1H, H–C(3)), 5.45 (d, br., J=12.4 Hz, 1H, H–C(10)), 4.34 (s, br., 1H, HO–C(11)), 4.08 (m, 2H, 2×H–CO)), 2.60, 2.50–1.70, 1.38 and 1.22 (dd and m each, 1H, 11H, 2H and 2H, J=3.6, 13.6 Hz, 7×CH_2 and 2×OH), 0.89 (s, 6H, $(CH_3)_2C(7)$). MS: 444/25 $[M]^+$, 426/15 $[M-H_2O]^+$, 231/55, 95/100. $C_{21}H_{30}F_6O_3$ (containing 0.29% of water and 2.92% of AcOEt) requires: C 56.69%, H 6.87%, F 24.90%; found: C 56.39%, H 7.09%, F 24.94%.

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References

1. Cancela, L.; Theofan, G.; Norman, A. W. *Hormones and Their Actions*, Cooke, B. A., King, R. J. B., Vander Moler, H. J., Eds.; Elsevier: New York, 1988; pp 269–289 (Part I, Chap. 15).
2. Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398.
3. Zhou, J.-Y.; Norman, A. W.; Akashi, M.; Chen, D.-L.; Uskokovic, M. R.; Aurrecoechea, J. M.; Dauben, W. G.; Okamura, W. H.; Koeffler, H. P. *Blood* **1991**, *78*, 75–82.
4. DeLuca, H. F. *FASEB J.* **1988**, 224–236.
5. Kragballe, K. *J. Cell. Biochem.* **1992**, *49*, 46–52.
6. Kutner, A.; Zhao, H.; Fitak, H.; Wilson, S. R. *Bioorg. Chem.* **1995**, *23*, 22–32.
7. Barbier, P.; Bauer, F.; Mohr, P.; Muller, M.; Pirson, W. WO 99/43646, priority date Feb. 26, 1998.
8. Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877–1952 (see 1933).
9. Perlman, K. L.; Swenson, R. E.; Paaren, H. E.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1991**, *32*, 7663–7666.
10. Zhou, X.; Zhu, G.-D.; Van Haver, D.; Vandewalle, M.; De Clercq, P. J.; Verstuyf, A.; Bouillon, R. *J. Med. Chem.* **1999**, *42*, 3539–3556.
11. Mikami, K.; Osawa, A.; Isaka, A.; Sawa, E.; Shimizu, M.; Terada, M.; Kubodera, M.; Nakagawa, K.; Tsugawa, N.; Okano, T. *Tetrahedron Lett.* **1998**, *39*, 3359–3362.
12. Courtney, L. F.; Lange, M.; Uskokovic, M. R.; Wovkulich, P. M. *Tetrahedron Lett.* **1998**, *39*, 3363–3366.
13. Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951–2954.
14. Negishi, E.; King, A. O.; Tour, J. M. *Org. Synth.* **1986**, *64*, 44–49.
15. de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174 (and references therein).
16. Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry* **1997**, *8*, 181–184.
17. Wirz, B.; Iding, H.; Hilpert, H. *Tetrahedron: Asymmetry* **2000**, *11*, 4171–4178.
18. Stetter, H.; Steinacker, K. H. *Chem. Ber.* **1952**, 451–454.
19. Roessler, F.; Hilpert, H. Results presented at the 12th International Congress on Catalysis on July 9th, 2000, in Granada, Spain.
20. Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640–3650.
21. Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669–5672.
22. Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811–814.
23. Suemune, M.; Takahashi, M.; Maeda, S.; Xie, Z.-F.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 425–428.
24. Dumortier, L.; Carda, J.; Van der Eycken, J.; Snatzke, G.; Vandewalle, M. *Tetrahedron: Asymmetry* **1991**, *2*, 789–792.
25. Hennig, M. Coordinates from X-ray analysis have been deposited at the Cambridge Crystallographic Data Centre, CCDC-No. 146699.
26. Sicinski, R. R.; Prahl, J. M.; Smith, C. M.; DeLuca, H. F. *J. Med. Chem.* **1998**, *41*, 4662–4674.
27. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178.
28. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357.
29. Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878.
30. Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863–3866.
31. Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100–2113.
32. Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955–968.
33. Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142.
34. Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *1*, 7–10.
35. Provencal, D. P.; Leahy, J. W. *J. Org. Chem.* **1994**, *59*, 5496–5498.
36. Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230–236.
37. Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.