Enantiospecific Synthesis of the (9*S*,18*R*)-Diastereomer of the Leukocyte Adhesion Inhibitor Cyclamenol A

Marc Nazaré[b] and Herbert Waldmann*[a]

Abstract: Cyclamenol A is one of the very few non-carbohydrate and non-peptide natural products that inhibit leukocyte adhesion to endothelial cells. We report on the first enantioselective total synthesis of the (9*S*, 18*R*)-diastereomer of this macrocyclic polyene lactam. Key elements of the synthesis are i) the synthesis of the required chiral building blocks by employing readily accessible building blocks from the chiral pool, that is, (*S*)-malic acid and (*R*)-hydroxyisobutyric acid, ii) assembly of a linear polyene precursor by means of Wittig and Horner olefination reactions as key C – C bond-forming transformations, iii) ring closure by means of a vanadium-mediated pinacolisation reaction and iv) conversion of the generated *cis*-diol into a (*Z*)-olefin to complete the entire polyene system of the natural product. Attempts to close the macrocyclic ring by a macrolactamisation, a double Stille coupling or direct olefination in a McMurry reaction failed. Crucial to the successful completion of the synthesis was the correct orchestration of the final steps. It was necessary to first deprotect the intermediate formed after macrocycle formation and to generate the sensitive heptaene system in the last step by means of a Corey–Hopkins sequence.

Keywords: bioorganic chemistry · leukocyte adhesion · medicinal chemistry · natural products · total synthesis

Introduction

The transport of leukocytes to the site of injury after inflammation and tissue infection is facilitated by their adhesion to endothelial cells.[1] However, over recruitment of these blood cells can result in the establishment of various diseases and disorders, and the inhibition of leukocyte adhesion to endothelial cells has recently received a lot of interest as a new strategy for the development of anti-inflammatory agents. This approach may offer entirely new and alternative opportunities for the treatment of many acute symptoms such as reperfusion injury, stroke, asthma and arthritis. For this purpose peptide- and carbohydrate derivatives in particular were developed as inhibitors of the selectin/sialyl Lewis X interaction.[2] However, non-peptide and non-carbohydrate natural products have not been investigated so far.

One of the very few natural products known to inhibit leukocyte adhesion to endothelial cells[3] is cyclamenol A.[4] This macrocyclic polyene lactam blocks this process in an ex vivo model and it completely inhibits adhesion of leukocytes to arterioles in hamsters (i.e., in vivo) at very low doses. Its mode of action and the structural parameters determining its biological activity, including the absolute configuration of the two stereogenic centres, are unknown.

In the light of these important and unsolved medicinal and biological questions, and in order to develop tools for unravelling the biological activity of cyclamenol A, we have embarked on a total synthesis of this natural product and analogues thereof. The purpose of this paper is to report on the first enantioselective total synthesis of the (9*S*, 18*R*)-diastereomer of cyclamenol A.[5]

Results and Discussion

Planning of the synthesis—retrosynthetic considerations: In developing an efficient strategy for a highly convergent route to the cyclamenol framework, several issues had to be considered. The unusual new polyene system present in cyclamenol A displays pronounced acid and base lability. This is particularly due to the tendency of the allylic hydroxyl group to be eliminated, with formation of a fully conjugated octaene system. Thus, after assembly of the entire backbone,

[a] Prof. Dr. H. Waldmann
Max-Planck-Institut für Molekulare Physiologie
Abteilung Chemische Biologie, Otto-Hahn-Str. 11
44227 Dortmund (Germany) and
Universität Dortmund, Fachbereich 3, Organische Chemie
44221 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de

[b] Dr. M. Nazaré
Aventis Pharma, Medicinal Chemistry G838
65926 Frankfurt (Germany)

  0947-6539/01/0715-3363 $ 17.50+.50/0

mild reaction conditions were mandatory. Furthermore, the results of molecular modelling experiments[6] at the PM3 level indicated that cyclamenol A has a rigid strained ring system (Figure 1). The cyclic perimeter of the natural product has a

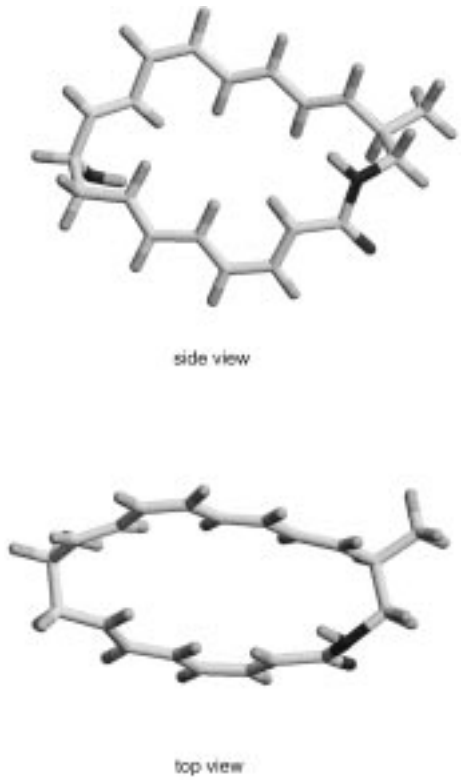
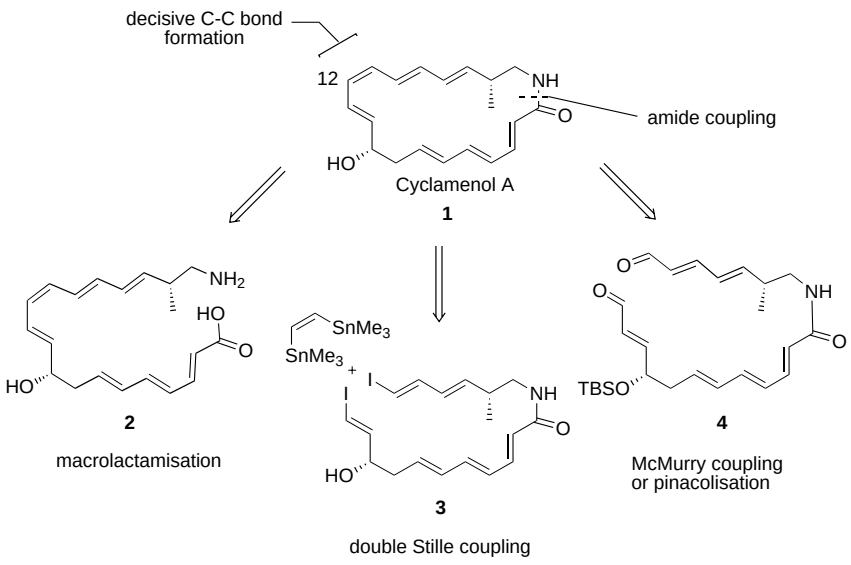


Figure 1. Structure of the (9*S*, 18*R*)-isomer of cyclamenol A as calculated on the PM3 level.

total of twenty bonds. The overwhelming majority of these are part of a triene and a tetraene system or of the amide bond, and display only a low tendency to become tilted out of the preferred conformation. Thus they form fairly rigid structural elements. More detailed investigations revealed that the *Z* configuration of the C(12)=C(13) double bond is essential to the stability of the macrocycle. The corresponding 12*E* isomer was calculated to be between 37 kJ mol^{-1} (PM3 calculation) and 50 kJ mol^{-1} (MM+ calculation) less stable. Consequently, it could be expected that, in spite of the danger of potential stereolability of the 12*Z* double bond, a subsequent isomerisation was not to be expected. In addition, even if the *E* double bond were formed, it should isomerise spontaneously to the more stable *Z* isomer.[7] The results of these calculations led to the notion that one of the key problems of the entire synthesis would be the appropriate choice and timing of the method and the conditions for closure and full establishment of the conformationally restricted, rigid polyene system of cyclamenol A. We planned to address this problem either by employing an amide-bond forming reaction in the last step or by establishing the entire backbone by formation of the C(12)=C(13) double bond (Scheme 1). For this latter approach, transition-metal-catalysed transformations like the Stille coupling, the McMurry reaction and the formation of pinacols from dialdehydes that allow both ends of the respective acyclic precursor to be tied together under template control were thought to be particularly attractive (Scheme 1).

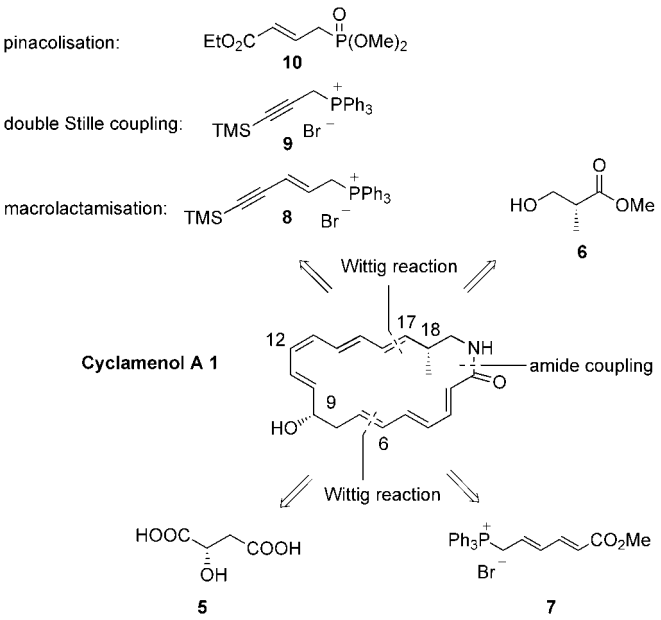
The absolute configuration of cyclamenol A is not known. In order to obtain a starting point for the synthesis a search of the Beilstein CrossFire database was undertaken. It revealed that in natural products with substructures identical or closely related to the structural units flanking the stereocentres of cyclamenol A, the absolute configuration that corresponds to the (9*S*, 18*R*)-diastereomer occurs with pronounced preference. Given the possibility of related biosynthetic origin, the (9*S*, 18*R*)-isomer of cyclamenol A was chosen as the target of the synthesis. We planned to introduce the stereocentres by employing readily accessible chiral building blocks from the chiral pool, that is, (*S*)-malic acid **5** and (*R*)-hydroxyisobutyric acid methyl ester **6**. For the assembly of the polyene substructures, Wittig and Horner–Emmons olefination reactions with phosphonium salts **8** and **9** and phosphonate **10** should serve as decisive synthetic transformations (Scheme 2). We planned to carry out the coupling of the resulting advanced intermediates by C–C bond formation at C(12) or by amide formation and, finally, the subsequent crucial ring-forming reaction would be executed vice versa by macrolactamisation or macrocyclisation by C–C bond formation at C(12).

The macrolactamisation approach: The synthesis of the C(12)-C(19) fragment commenced with amino alcohol **12** which is readily accessible from (*R*)-hydroxyisobutyric acid methyl ester **6** in two steps[8] (Scheme 3). Subsequent selective



Scheme 1. Retrosynthetic alternatives for the final ring-closing reaction.

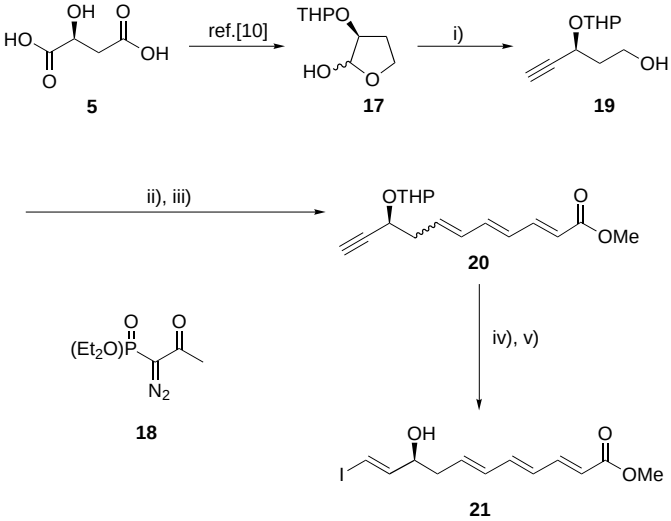
0947-6539/01/0715-3364 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15



Scheme 2. Retrosynthetic dissection of cyclamenol A to obtain building blocks for the assembly of advanced intermediates.

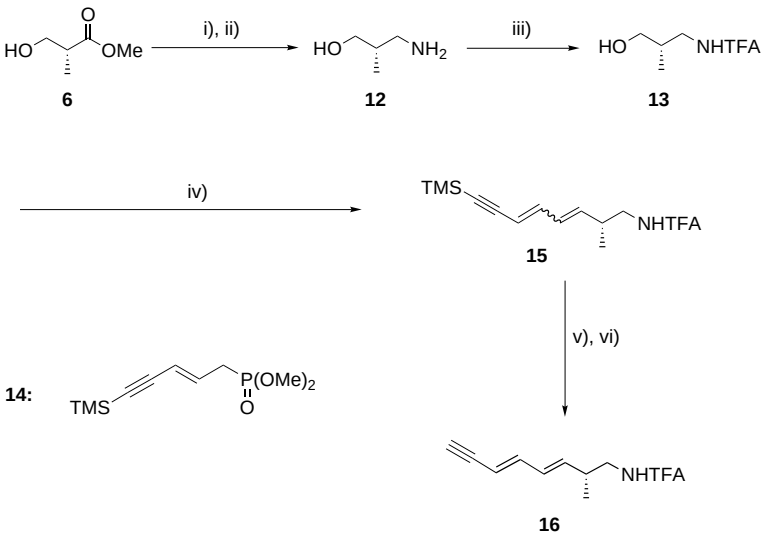
protection of the amine as trifluoroacetamide and oxidation of the alcohol under Swern conditions yielded the corresponding masked aminoaldehyde, which was employed for chain elongation by an olefination reaction. Treatment with deprotonated phosphonium bromide **8**[9] gave dienyne **15** in high yield, however, as a 1:1 mixture of *E*/*Z*-diastereomers. Use of the corresponding Horner–Emmons reagent **14** led to a 3:1 mixture of the *E* and *Z* olefin. However, the isomers could be readily separated, and the *Z*-compound could be isomerised to the desired *E*-diastereomer by treating it with catalytic amounts of iodine. Finally, removal of the TMS group yielded the desired C(12)-C(19) building block **16**.

The synthesis of the C(1)-C(11) unit **21** commenced with lactol **17** which is readily available from (*S*)-malic acid **5** (Scheme 4). To this end, the aldehyde, liberated from lactol **17** in equilibrium, was coupled with diazo ketophosphonate **18**[11] to give alkyne **19**. Subsequent chain elongation by means of a Swern–Wittig sequence by using phosphonium salt **7**[12]



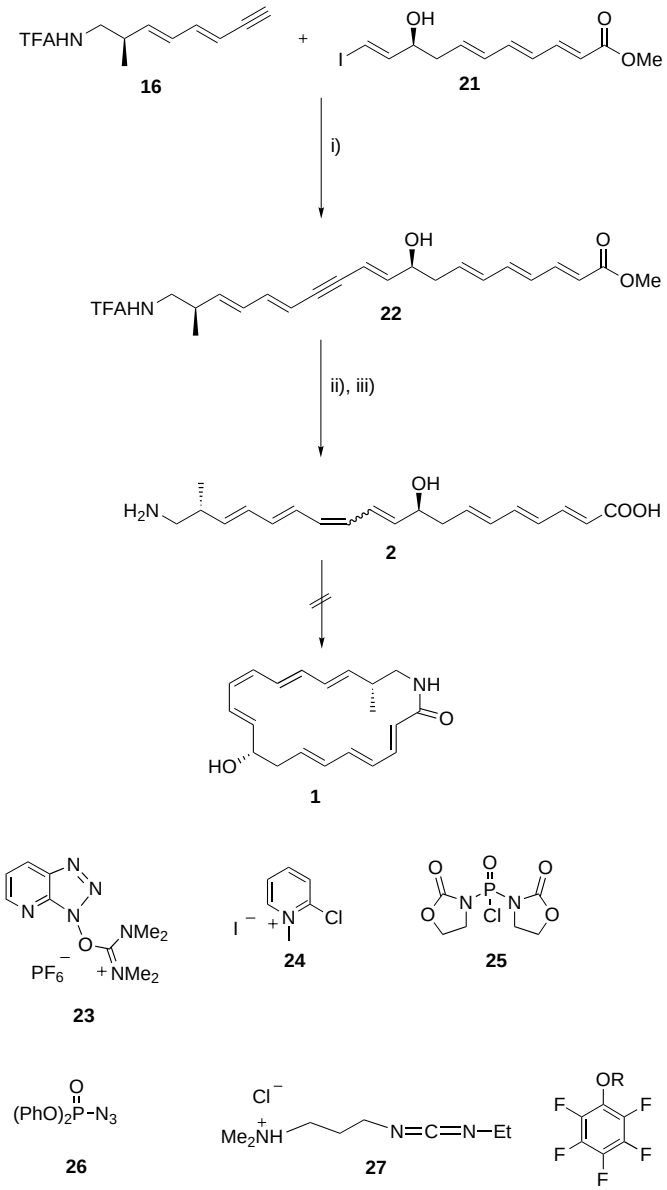
Scheme 4. Synthesis of vinyliodide intermediate **21** from (*S*)-malic acid **5**. i) **18**, K_2CO_3, MeOH, RT, 80%; ii) $(COCl)_2$, DMSO, NEt_3, iii) **7**, *n*BuLi, THF, −78°C to RT, 82%, two steps; iv) PPTS, MeOH, 45°C, →**20b**, 88%; v) Bu_3SnH; $Pd(PPh_3)_4$, RT, CH_2Cl_2, then I_2, −20°C, 68%.

yielded the triply unsaturated methyl ester **20** (*E*/*Z* = 4:1). From **20** the tetrahydropyran (THP) protecting group could be removed in high yield without dehydration. However, under these acidic conditions the 9*Z* isomer gratifyingly isomerised to the desired *E* compound. Finally, the alkyne was subjected to a regio- and stereoselective palladium-catalysed hydrostannylation reaction[13] and the resulting (*E*)-vinyl stannane was converted into (*E*)-vinyl iodide **21** by means of metal-halogen exchange. Alkyne **16** and vinyl iodide **21** were then coupled in a Sonogashira reaction to give the complete carbon backbone **22** of cyclamenol (Scheme 5). Whereas compound **22** proved to be fairly stable, the polyene obtained after *Z*-selective reduction of the alkyne with activated zinc[15] was substantially more labile. This sensitivity was even more pronounced for seco acid **2**, which was obtained after simultaneous removal of the amino- and carboxy protecting groups.



Scheme 3. Synthesis of dienyne **16** from (*R*)-hydroxyisobutyric acid methyl ester. i) NH_3, MeOH, NaCN, 50°C; ii) $BH_3 \cdot Me_2S$, THF, reflux 78%, two steps; iii) Trifluoro acetic anhydride, CH_2Cl_2 90%; iv) $(COCl)_2$, DMSO, NEt_3 **8**, *n*BuLi, THF, −78°C to RT, 77% or **14**, LDA, THF, −78°C, 65%; v) I_2(cat.), CH_2Cl_2, daylight, 80%; vi) $AgNO_3$, KCN, EtOH/H_2O 90%.

Linear congener **2** was then subjected to a variety of cyclisation protocols established for macrolactonisation and -lactamisation reactions. However, neither the use of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetra-



Scheme 5. Attempted synthesis of target compound **1** by macrolactamisation as final ring-closing step. i) $Pd(PhCN)_2Cl_2$, CuI, piperidine, PhH, 87%; ii) Zn(Cu/Ag), MeOH → **22b**, 55%; iii) LiOH, THF/MeOH/H_2O, 40%.

methyluronium hexaflurophosphate (HATU) **23**,[16] 2-choro-*N*-methylpyridinium iodide **24**,[17] bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl) **25**,[18] diphenylphosphoryl azide (DPPA) **26**[19] or the formation of a pentafluorophenyl ester with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) **27**[20a] under different conditions yielded the desired macrolactam **1**. This complete failure of cyclisation by lactam formation is most likely due to a combination of several parameters. Firstly, once the entire tetra- and triene system is established, the cyclisation precursor becomes rather unstable; this results in degradation. This indicated that the complete polyene system should only be established in the very late steps of the synthesis (see below). Secondly, as subsequent investigations revealed (see also below), trienic carboxylic acids display only low reactivity and require strong activating reagents and conditions, a precondition which might not have been fulfilled by reagents **23**–**26**. Finally, the 12*Z*-double bond incorporated into seco acid **2** may be sensitive to isomerisation, and modelling experiments revealed that the corresponding *E* isomer cannot be cyclised for geometric reasons.

The double Stille coupling approach: The conclusion from the failure of the macrolactamisation approach, that the 12*Z* double bond should be established as late as possible in the synthesis and stabilised by the preferred configuration of the macrocycle (see the results of the calculations described above), prompted us to investigate a double Stille reaction as the key transformation. Such a strategy has been successfully introduced and employed for ring closure by Nicolaou et al.[21] in the synthesis of rapamycin.

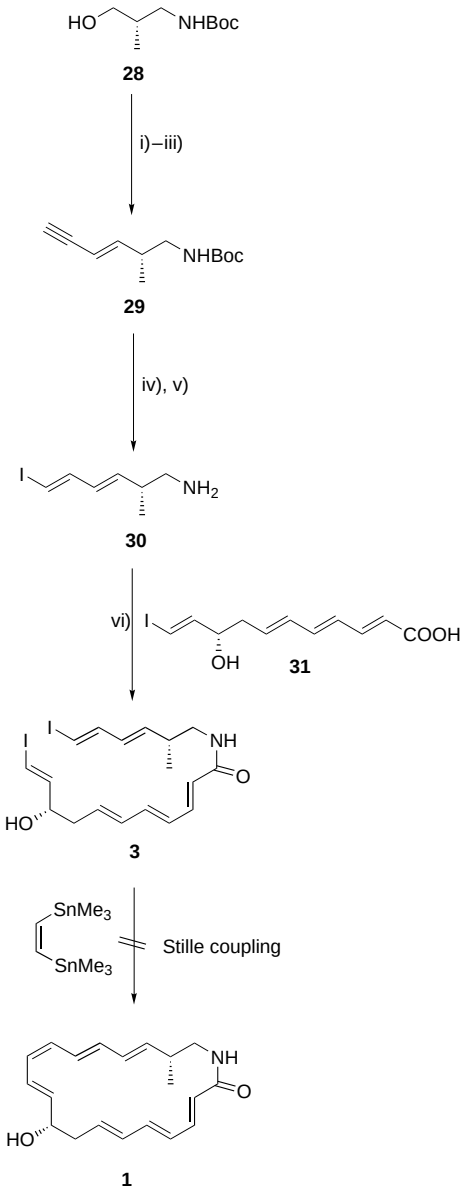
Due to the modular conception of the synthesis plan, the bis-vinyl iodide precursor **3** was readily accessible from building blocks whose synthesis had already been established in the macrolactamisation approach. As shown in Scheme 6, C(14)-C(19) fragment **30** was synthesised from aminoalcohol **28**.[8] Swern oxidation, a stereoselective Wittig reaction with phosphonium salt **9** and subsequent deprotection of the acetylene delivered (*E*)-eneyne **29**. This intermediate was then subjected to a hydrozirconation reaction,[22] and the organometallic intermediate formed thereby was iodinated to give the corresponding isomerically homogeneous dienyliodide. After removal of the Boc group with TMSOTf buffered with lutidine, unprotected amine **30** was coupled with acid **31** by using diethylphosphoryl cyanide[20b,c] as coupling reagent. Acid **31** was obtained by saponification of methyl ester **21** with LiOH (see Experimental Section).

Bis-vinyl iodide **3** obtained by this reaction sequence was then subjected to the planned Stille coupling with (*Z*)-1,2-*bis*(trimethylstannyl)ethylene[23] (see Scheme 6). However, under a variety of well-established reaction conditions and by employing different catalyst systems[24a,b] like $Pd_2(dba)_3$/Ph_3As or $Pd(PhCN)_2Cl_2$/Ph_3As a ring closure could not be achieved. In these reactions, starting material **3** was completely consumed but, unfortunately, the olefinic structural elements were largely destroyed and oligomeric products were formed.

This failure most likely is due to the sensitivity of the compounds employed. Furthermore, molecular modelling experiments indicated that precursor **3** preferably adopts the *S-trans* conformation of the amide. In this conformation, the two vinyl iodide termini point away from each other. In addition, palladium template control is not usually pronounced,[24c–e] so that under these conditions the required preorientation of the reacting centres may not be achievable.

The McMurry and pinacolisation approaches: In the light of the results detailed above for the decisive ring closure reaction, a transformation was sought that would be characterised by a more pronounced template effect. We resorted to the McMurry and pinacolisation approaches, for which it is known that the low-valent metal centres generated in these transformations strongly precoordinate the aldehyde groups required. Retrosynthetic analysis identified aminoalcohol **28** and butanetriol **34**, which is accessible from (*S*)-malic acid, as

  0947-6539/01/0715-3366 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15

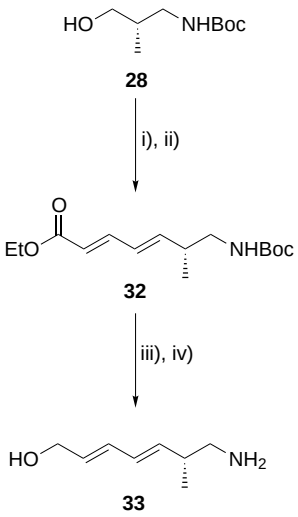


Scheme 6. Attempted synthesis of target compound **1** by double Stille coupling as final ring-closing step. i) $(COCl)_2$, DMSO, NEt_3; ii) **9**, *n*BuLi, THF, →**28b**, 72%, two steps; iii) K_2CO_3, MeOH, 93%; iv) Cp_2ZrCl_2/$LiBEt_3H$ then I_2, →**29b**, 75%; v) TMSOTf, lutidine, 90%; vi) $(EtO)_2$-POCN, NEt_3, DMF, 74%.

the key building blocks. The key question was whether the highly unsaturated diallylic alcohol or dialdehyde intermediate to be generated would be sufficiently stable to allow for investigation of the planned transformation.

The C(13)-C(19) fragment **33** was built up in a short and efficient sequence from protected amino alcohol[8] **28** (Scheme 7). Swern oxidation of the primary alcohol and chain elongation with crotonoyl-phosphonate **10** yielded doubly unsaturated ester **32**, which was reduced to the allylic alcohol. Removal of the Boc group and extractive workup with K_2CO_3 solution gave amino alcohol **33** in high yield. It was used directly for the subsequent steps.

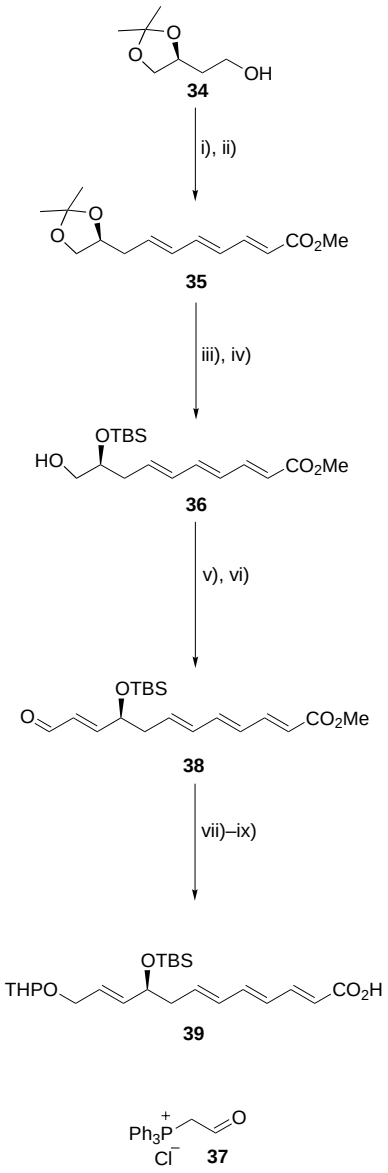
The C(1)-C(12) fragment was synthesised from selectively protected butanetriol **34**[34] by two successive elongations of



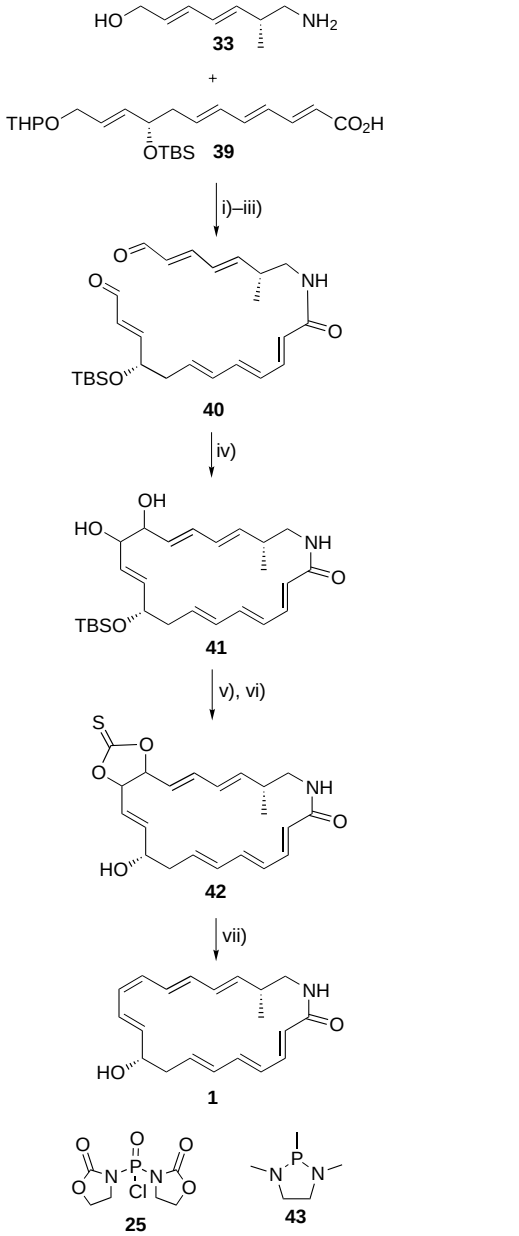
Scheme 7. Synthesis of advanced building block **33** from selectively protected amino alcohol **28**. i) $(COCl_2)$, DMSO, NEt_3; ii) **10**, LDA, −78 °C to RT, 83% for two steps; iii) DIBAH; CH_2Cl_2, −78 °C to −30 °C, →**32b**, 90%; iv) TFA/CH_2Cl_2 3:5, 0 °C, then aq. K_2CO_3, 84%.

the carbon chain (Scheme 8). First, the primary alcohol **34** was converted to the corresponding, unstable aldehyde by Swern oxidation; this aldehyde was then treated with the ylide, which had been formed in situ from the phosphonium salt **7** (derived from sorbic acid) by deprotonation with butyllithium. The diol obtained after removal of the acetonide from **35** was rather unstable; thus, it was immediately converted to the bis-silylether. Then the more labile *tert*-butyldimethylsilyl ether of the primary alcohol was cleaved selectively by treatment with a solution of pyridinium hydrofluoride in a mixture of pyridine and THF at room temperature. The selectively unmasked and highly unsaturated alcohol **36** was obtained in high overall yield. It was then subjected to a one-pot reaction sequence that included oxidation of the alcohol to the aldehyde and Wittig reaction with formylmethylenetriphenylphosphonium chloride, **37**, in the presence of NEt_3. In this way the need to isolate the very unstable α-alkoxyaldehyde intermediate was circumvented. The significantly more stable α,β-unsaturated aldehyde **38** could be isolated in high yield.

For the amide linkage of the C(1)-C(12) and C(13)-C(19) fragments, the aldehyde group in **38** had to be reduced, and the resulting allylic alcohol was masked as a THP ether, which is orthogonally stable to the TBS ether and the methyl ester in **38**. This protection proved to be necessary, since the unmasked primary alcohol interfered with the subsequent formation of the amide bond. After saponification of the methyl ester, the resulting carboxylic acid was preactivated by treatment with BOP-Cl. The activated intermediate reacted chemoselectively with amino alcohol **33** to yield the desired amide in high yield (Scheme 9). Strong preactivation with BOP-Cl was necessary to achieve a high yield in this step, since tetraene carboxylic acid **39** is only moderately reactive. The use of carbodiimide/1-hydroxybenzotriazole (HOBt) or HATU was not successful or gave markedly lower yields. Next the THP ether was removed, and the bis-allylic alcohol was oxidised with perruthenate to give the moderately stable



Scheme 8. Synthesis of advanced building block **39** from selectively protected triol **34**. i) $(COCl)_2$, DMSO, CH_2Cl_2, $-78\,^{\circ}C$, NEt_3; ii) **7**, *n*BuLi, THF, $0\,^{\circ}C$ to RT, 85% for two steps; iii) TosOH; MeOH, RT, then TBSCl, imidazole, DMF, $\rightarrow$**35b**, 82%; iv) HF·py, pyridine, THF, RT, 73%; v) $(COCl)_2$, DMSO, CH_2Cl_2, $-78\,^{\circ}C$, NEt_3; vi) **37** NEt_3, CH_2Cl_2, RT, 70% for two steps; vii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, *i*PrOH, $0\,^{\circ}C$, $\rightarrow$**38b**, 77%; viii) PPTS, DHP, CH_2Cl_2, RT, $\rightarrow$**38c**, 93%; ix) $LiOH \cdot H_2O$, THF/MeOH/H_2O, 72%.



Scheme 9. Synthesis of (9*S*, 18*R*)-cyclamenol by means of pinacolisation and subsequent olefin formation as the key steps. i) **25** NEt_3, THF, DMAP $\rightarrow$**39b**, 75%; ii) PPTS, *i*PrOH; $55\,^{\circ}C$, $\rightarrow$**39c**, 73%; iii) NMO, nPr_4RuO_4, 3 Å MS, CH_2Cl_2, RT, 78%; iv) $VCl_3 \cdot (THF)_3$, Zn, THF, 12 h, high dilution, RT, 60%; v) $CSCl_2$, DMAP, CH_2Cl_2, $0\,^{\circ}C$, $\rightarrow$**41b**, 65%; vi) TBAF, HOAc, THF, RT, 26%; vii) **43**, Et_2O, $-20\,^{\circ}C$, 20%.

dialdehyde intermediate **40**. Use of the Swern oxidation or MnO_2 was not successful.

Having achieved the crucial intermediate **40**, in a first series of experiments we focussed on the McMurry reaction to generate the 20-membered macrocycle. Disappointingly, this direct olefination with the $TiCl_3 \cdot (DME)_2$ complex together with potassium,[26a] lithium aluminium hydride,[26b] or a zinc-copper couple[26c] as reducing reagents, as well as $TiCl_4$ with zinc,[26d] a zinc-copper couple[26e] or lithium aluminium hydride[26f] together with amine bases was not successful.

As an alternative, a two-step sequence consisting of a pinacolisation reaction and subsequent olefin formation by elimination was investigated. However, titanium-mediated pinacol formation[27] under a variety of reaction conditions ($TiCl_4$, Mg/Hg, THF; $TiCl_3$ Zn or Mg, TMSCl, *t*BuOH/THF; Cp_2TiCl_2, Zn or Mg, THF) and SmI_2-mediated[28] coupling were not successful either. Finally, vanadium was chosen as the metal and, after substantial experimentation, the use of the vanadium reagent $[V_2Cl_3 \cdot (THF)_6] \cdot [Zn_2Cl_6]$[29] (prepared in situ) under high dilution conditions in THF met with success. These conditions afforded the cyclic pinacol **41** in 60% yield. Notably, the use of THF as solvent is mandatory; if CH_2Cl_2 or CH_2Cl_2/DMF mixtures were used as solvent, product formation was not observed. After this crucial step had been accomplished attention was focussed on finding

0947-6539/01/0715-3368 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15

proper and gentle reaction conditions for generating the sensitive polyene system and for the deprotection of the secondary alcohol.

For the conversion of the vicinal diol into an olefin, first a route via the corresponding bis-mesylate was investigated—without success. As an alternative, the Corey–Hopkins method was employed,[30] and to this end, the pinacol was converted into the thionocarbonate by treatment with thiophosgene and 4-dimethylamino pyridine (DMAP). After chromatographic purification, NMR spectroscopic investigation permitted the relative configuration of the diol unit to be assigned. Thus, the ^{1}H NMR spectrum of the *O*-silylated thionocarbonate obtained from diol **41** displayed a coupling constant of 7 Hz for the two CH(OCS) signals of the five-membered ring. This indicated that the two hydrogen atoms are *cis*-oriented (in related compounds coupling constants of 6.5–7.8 Hz are found[31]). In addition, since the planned subsequent elimination of thionocarbonates to olefins is known to be a stereospecific *syn*-elimination, it was clear that the *cis*-olefin would be formed.

Crucial to the success of the synthesis was the order in which the final steps were carried out. Thus, in a first approach, the final C(12)-C(13) double bond was generated, and then we attempted to cleave the silyl ether group. However, once the heptaene is established, protected cyclamenol A becomes very sensitive to both acid and base. Attempts to cleave the silyl ether by treatment with $NEt_3 \cdot 3HF$[32] in THF, NH_4F in methanol, tris(dimethylamino)sulfonium difluorotrimethyl silicate (TASF)[33] in acetonitrile or DMF, as well as particularly efficient fluoride sources like TBAF in THF (in the absence or presence of acetic acid) and HF·pyridine in THF or methanol only resulted in decomposition of the protected intermediate. Finally, the solution was to reverse the order in which the two last steps were carried out. First, the silyl protecting group was removed by treating the protected thionocarbonate with TBAF/AcOH to give secondary alcohol **42** in moderate yield (Scheme 9). Then the fragmentation of the thionocarbonate was induced with trimethyldiazaphospholidine **43**[30b] yielding (9*S*, 18*R*)-cyclamenol A.

Comparison of the spectroscopic data recorded for the synthetic sample with the data obtained for the natural product clearly proved that the desired cyclic polyene system had been formed. However, whereas naturally occurring cyclamenol A[4] displays a specific rotation of $[\alpha]_D^{20} = +1000^\circ$ ($c = 0.01$ in DMF) we measured a value of $[\alpha]_D^{20} = +60^\circ$ ($c = 0.01$ in DMF) for the synthetic compound. Thus, the natural product does not have the (9*S*,18*R*)-configuration. We stress, however, that the enantiomers of the chiral building blocks are readily available; this implies that the other diastereomers of the natural product would also be accessible by the route detailed above.

Conclusion

In conclusion, we have developed a synthesis of the (9*S*,18*R*)-diastereomer of the leukocyte adhesion inhibitor cyclamenol A. The synthesis is highly convergent and proceeds with high efficiency, that is, the longest linear sequence consists of ten steps and relays the stereogenic centres of the polyene macrolactam to two building blocks from the chiral pool that are readily available in both enantiomeric forms. The flexibility and convergent character of the synthetic route will give access to all diasteromers of the natural product, as well as to various analogues with improved stability and altered biological properties. This synthesis now provides the opportunity to develop a new class of non-carbohydrate and non-peptidic inhibitors of leukocyte adhesion to endothelial cells.

Experimental Section

General Procedures: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250, AM400 or DRX500 spectrometer at room temperature. Mass spectra and high-resolution mass spectra (HRMS) were measured on a Finnigan MAT MS70 spectrometer. The optical rotation was determined with a Perkin-Elmer Polarimeter 241.

Materials: All reactions were performed under an argon atmosphere with freshly distilled and dried solvents. The solvents were dried by standard methods. Silica gel (40–60 μm) was used for column chromatography. Commercial reagents were used without further purification.

Numbering of the cyclic compounds: For reasons of the consistency the numbering of the cyclic compounds starts at the amidic carbonyl group.

***N*1-[(2*S*)-3-Hydroxy-2-methylpropyl]-2,2,2-trifluoroacetamide (13)**: Trifluoroacetic anhydride (2.1 mL, 17 mmol) was carefully added at $-10\,^\circ$C to a solution of amino alcohol **12**[8] (508 mg, 5.7 mmol) and NEt_3 (4.6 mL, 33.6 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was warmed to room temperature and stirred for 2 h. Then K_2HPO_4 buffer at pH 7 (20 mL) and MeOH (20 mL) were added and the mixture was stirred for 1 h. Finally, the mixture was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried over Na_2SO_4. After removal of the solvents under reduced pressure, the residue was filtered through a plug of silica with ether/pentane (2:1) to yield a colourless oil. Yield: 947 mg (5.1 mmol), 90%; TLC: $R_f = 0.43$ (ether); $[\alpha]_D^{20} = +3.2$ ($c = 1.2$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.70$ (br s, 1H; NH), 4.35 (dd, $^2J = 11$ Hz, $^3J = 4$ Hz, 1H; H-1), 4.24 (dd, $^2J = 11$ Hz, $^3J = 4$ Hz, 1H; H-1), 3.41 (m, 1H; H-3), 3.35 (m, 1H; H-3), 2.27 (sext, $^3J = 4$ Hz, 1H; H-2), 1.95 (br s, 1H; OH), 1.06 (d, $^3J = 7$ Hz, 3H; Me-2); ^{13}C NMR (125.5 MHz, $CDCl_3$): $\delta = 155.3$ (q, $J =$ 37 Hz, quart. C, C=O), 117.7 (q, $J = 288$ Hz, quart. C, CF_3), 70.2 (CH_2, C(1)), 42.5 (CH_2, C(3)), 32.7 (CH, C(2)), 14.3 (CH_3, Me-2).

***N*1-[(2*R*,3*E*,5*E*)-2-Methyl-8-(1,1,1-trimethylsilyl)-3,5-octadien-7-ynyl]-2,2,2-trifluoroacetamide (15)**

Wittig reaction: A solution of DMSO (1.4 mL, 19 mmol) in CH_2Cl_2 (5 mL) was added dropwise at $-78\,^\circ$C to a solution of oxalylchloride (0.9 mL, 9 mmol) in CH_2Cl_2 (30 mL). After 30 min, a solution of alcohol **13** (1.0 g, 5.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise, and the reaction mixture was stirred for 1 h. Finally, NEt_3 (3.6 mL, 28 mmol) was added and the mixture was allowed to warm slowly to $0\,^\circ$C. After completion of the reaction (TLC control), water (100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude aldehyde (1 g, 5.7 mmol) was directly subjected to the following Wittig reaction:

*n*BuLi (3.4 mL, 8.3 mmol, 2.5 M in hexanes) was added dropwise at $-78\,^\circ$C too a vigorously stirred suspension of phosphonium salt **8**[9] (4.1 g, 8.3 mmol) in THF (100 mL). After 10 min, the reaction mixture was allowed to warm to $0\,^\circ$C and then cooled again to $-78\,^\circ$C. Then the crude aldehyde (~5.7 mmol) was slowly added and the reaction mixture was allowed to warm to room temperature overnight. After removal of the solvents under reduced pressure, the residue was triturated with ether ($6 \times$ 100 mL). The solvent of the combined organic layers was removed, and the residue was then purified by chromatography (cyclohexane/ethyl acetate 4:1) to afford a yellow oil. Yield: 1.3 g (4.3 mmol), 77%. The *E*/*Z* isomeric ratio was determined by comparison of the characteristic ^{1}H NMR signals

of crude **15**: *E/Z* = 1:1. *Z* isomer ***Z*-15**: 6.15 (t, ^3J = 11 Hz, H-4), 5.53 (dd, ^3J = 11 Hz, ^3J = 8 Hz, H-3). *E* isomer **15**: 6.11 (dd, ^3J = 16 Hz, ^3J = 10 Hz, H-4), 5.65 (dd, ^3J = 16 Hz, ^3J = 10 Hz, H-3).

Horner–Emmons reaction: A solution of DMSO (0.9 mL, 12 mmol) in CH_2Cl_2 (5 mL) was added dropwise at −78 °C to a solution of oxalylchloride (0.56 mL, 5.6 mmol) in CH_2Cl_2 (20 mL). After 30 min, a solution of alcohol **13** (600 mg, 3.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture was allowed to stir for 1 h. Finally, NEt_3 (2.2 mL, 17 mmol) was added, and the mixture was allowed to warm slowly to 0 °C. After completion of the reaction (TLC control), water (100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude aldehyde (600 mg, 3.2 mmol) was directly subjected to the following Horner–Emmons reaction:

*n*BuLi (2.4 mL, 6 mmol, 2.5 M in hexanes) was added dropwise at −78 °C to a solution of diisopropylamine (0.87 mL, 6.2 mmol) in THF (10 mL). After 30 min at −78 °C, the solution was warmed to 0 °C for 10 min and cooled again to −78 °C. This lithium diisopropylamide (LDA) solution was transferred dropwise at −78 °C to a solution of phosphonate **14** (1.5 g, 6 mmol) in THF (70 mL). Within 1 h the reaction mixture was allowed to warm to −20 °C and then cooled again to −78 °C. The aldehyde (~3.2 mmol) in THF (8 mL) was added dropwise to this solution, and the reaction mixture was allowed to warm to −40 °C. After 3 h at this temperature, the reaction was diluted with ether (20 mL) and quenched by addition of saturated NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, and the solvents removed under reduced pressure. The residue was purified by chromatography with cyclohexane/ethyl acetate (4:1) to give a yellow oil. Yield: 636 mg (2.1 mmol), 65 %; TLC: R_f (*E* isomer) = 0.36 (cyclohexane/ethyl acetate 4:1), R_f (*Z* isomer) = 0.42 (cyclohexane/ethyl acetate 4:1). The *E/Z* isomeric ratio was determined by comparison of the characteristic signals of crude **15**: *E/Z* = 3:1. *Z* isomer ***Z*-15**: 6.15 (t, ^3J = 11 Hz, H-4), 5.53 (dd, ^3J = 11 Hz, ^3J = 8 Hz, H-3). *E* isomer **15**: 6.11 (dd, ^3J = 16 Hz, ^3J = 10 Hz, H-4), 5.65 (dd, ^3J = 16 Hz, ^3J = 10 Hz, H-3).

Isomerisation: Two crystals of iodine were added to a solution of the *E/Z* isomer mixture of **15** (830 mg, 2.7 mmol) in CH_2Cl_2 (70 mL), and the flask was exposed to direct sunlight for one day. The solution was then washed with saturated $Na_2S_2O_3$ solution (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, R_f = 0.36) to afford a yellow oil. Yield: 664 mg (2.2 mmol), 80 %; $[\alpha]_D^{20}$ = +15.8 (*c* = 1 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.58 (dd, ^3J = 16 Hz, ^3J = 10 Hz, 1 H; H-5), 6.28 (m, 1 H; NH), 6.11 (dd, ^3J = 16 Hz, ^3J = 10 Hz, 1 H; H-4), 5.65 (dd, ^3J = 16 Hz, ^3J = 8 Hz, 1 H; H-3), 5.61 (d, ^3J = 16 Hz, 1 H; H-6), 3.42 (m, 1 H; H-1), 3.25 (m, 1 H; H-1), 2.51 (m, 1 H; H-2), 1.08 (d, ^3J = 7 Hz, 3 H; Me-2), 0.19 (s, 9 H; $SiMe_3$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): δ = 157.3 (q, *J* = 37 Hz, quart. C, C=O, TFA), 141.8 (CH, C3), 138.1 (CH, C5), 130.4 (CH, C4), 118.3 (q, *J* = 283 Hz, quart. C, CF_3), 111.2 (CH, C6), 104.0 (quart. C, C8), 94.5 (quart. C, C(7)), 44.7 (CH_2, C(1)), 37.1 (CH, C(2)), 17.2 (CH_3, Me-2), -0.1 (CH_3, $SiMe_3$); MS (EI, 70 eV): *m/z* (%): 303 (13) [M^+], 190 (391), 179 (27), 175 (30), 126 (13), 97 (36), 73 (100); HRMS-EI (70 eV): calcd for $C_{14}H_{20}F_3NOSi$: 303.1266, found: 303.1248.

***N*1-[(2*R*,3*E*,5*E*)-2-Methyl-3,5-octadien-7-ynyl]-2,2,2-trifluoroacetamide (16)**: A solution of $AgNO_3$ (1.8 g, 11 mmol) in a mixture of ethanol (10 mL) and water (10 mL) was added dropwise at 0 °C to a solution of alkyne **15** (1.1 g, 3.6 mmol) in EtOH (10 mL) and THF (5 mL). The reaction mixture was stirred for 3 h at room temperature. Finally, a solution of KCN (4.8 g, 74 mmol) in water (10 mL) was added. After 40 min, the reaction mixture was extracted with ether (3 × 100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, R_f = 0.32) to afford a yellow oil. Yield: 740 mg (3.2 mmol), 90 %; $[\alpha]_D^{20}$ = +20.2 (*c* = 1 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.55 (dd, ^3J = 16 Hz, ^3J = 10 Hz, 1 H; H-5), 6.24 (m, 1 H; NH), 6.12 (dd, ^3J = 16 Hz, ^3J = 10 Hz, 1 H; H-4), 5.63 (dd, ^3J = 16 Hz, ^3J = 8 Hz, 1 H; H-3), 5.60 (d, ^3J = 16 Hz, 1 H; H-6), 3.42 (m, 1 H; H-1), 3.25 (m, 1 H; H-1), 2.27 (s, 1 H; H-8), 2.51 (m, 1 H; H-2), 1.08 (d, ^3J = 7 Hz, 3 H; Me-2); ^{13}C NMR ($CDCl_3$, 125.5 MHz): δ = 157.1 (q, *J* = 37 Hz, quart. C, C=O, TFA), 145 (CH, C(8)), 141.2 (CH, C(3)), 138.0 (CH, C(5)), 130.4 (CH, C(4)), 118.3 (q, *J* = 283 Hz, quart. C, CF_3), 111.2 (CH, C(6)), 96.3 (quart. C, C(7)), 44.6 (CH_2, C(1)), 37.5 (CH, C(2)), 17.2 (CH_3, Me-2); MS (EI, 70 eV): *m/z* (%): 231 (18) [M^+], 149 (16), 126 (32), 118 (100), 117 (47), 105 (50), 103 (42), 91 (14), 79 (44), 77 (43); HRMS-EI (70 eV): calcd for $C_{11}H_{12}F_3NO$: 231.0871, found: 231.0882.

(3*S*)-3-(Tetrahydroxy-2*H*-2-pyranyloxy)tetrahydro-2-furanol[10] (17): Diisobutyl aluminium hydride (DIBAH) (17.7 mL; 1 M in hexanes, 17.7 mmol) was slowly added at −78 °C to a solution of (3*S*)-3-(tetrahydroxy-2*H*-2-pyranyloxy)tetrahydro-2-furanone[10] (2.5 g, 13 mmol) in CH_2Cl_2 (100 mL). After 3 hour's stirring, the reaction mixture was quenched by addition of MeOH (10 mL) and warmed to room temperature. After 1 h, saturated Na-,K-tartrate solution (20 mL) was added and the mixture was stirred further until clarification of the phases. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography (ether/pentane 2:1) giving a colourless oil. Yield: 2.2 g (12 mmol), 88 %; TLC: R_f = 0.26 (cyclohexane/ethyl acetate 3:2); $[\alpha]_D^{20}$ = +4.7 (*c* = 1.4 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 5.27 (s, 1 H; H-2), 4.65 (m, 1 H; OCHO, THP), 4.17 (m, 1 H; H-3), 4.10 (m, 1 H; H-5), 4.00 (t, ^3J = 8 Hz, 1 H; H-5), 3.70 (m, 1 H; OCH, THP), 3.45 (m, 1 H; OCH, THP), 2.68–1.82 (m, 2 H; H-4), 1.72 (m, 2 H; THP), 1.47 (m, 4 H; THP); MS (EI, 70 eV): *m/z* (%): 189 (0.1) [M^+ + H], 171 (0.1), 159 (0.2), 140 (0.1), 128 (0.2), 115 (2), 101 (10), 85 (100), 69 (19), 57 (16); HRMS-EI (70 eV): calcd for $C_9H_{17}O_4$: 189.1127 found: 189.1144.

(3*S*)-3-(Tetrahydroxy-2*H*-2-pyranyloxy)-4-pentyn-1-ol (19): Phosphonate **18**[11] (621 mg, 3.2 mmol) was added at room temperature to a suspension of lactol **17** (400 mg, 2.1 mmol) and K_2CO_3 (753 mg, 5.4 mmol) in MeOH (50 mL), and the solution was stirred overnight. The reaction mixture was then diluted with ether (200 mL), washed with water (30 mL) and finally dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by chromatography (ether/pentane 2:1, R_f = 0.25) to give a colourless oil. Yield: 310 mg (1.7 mmol), 80 %; $[\alpha]_D^{20}$ = −47.5 (*c* = 0.3 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.87 (s, 1 H; OCHO, THP), 4.61 (t, ^3J = 6 Hz, 1 H; H-3), 3.85 (t, ^3J = 3 Hz, 1 H; OCH, THP), 3.74 (q, ^3J = 6 Hz, 2 H; H-1), 3.50 (m, 1 H; OCH, THP), 2.37 (d, ^4J = 2 Hz, 1 H; H-5), 1.96 (m, 2 H; H-2), 1.64 (m, 2 H; THP), 1.50 (m, 4 H; THP); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 96.3 (CH, THP), 82.0 (quart. C, C(4)), 73.9 (CH, C(3)), 63.6 (CH, C(5)), 63.0 (CH_2, C(2)), 59.7 (CH_2, C(1)), 37.7 (CH_2, THP), 30.4 (CH_2, THP), 25.2 (CH_2, THP), 19.6 (CH_2, THP); MS (EI, 70 eV): *m/z* (%): 183 (0.6) [M^+-H], 153 (2), 150 (3), 149 (70), 109 (31), 102 (10), 85(100), 79 (10); HRMS-EI (70 eV): calcd for $C_{10}H_{15}O_3$: 183.1021 found: 183.1012.

Methyl(2*E*,4*E*,6*E*,9*S*)-9-(tetrahydroxy-2*H*-2-pyranyloxy)-2,4,6-undecatrien-10-ynoate (20): A solution of DMSO (6.2 mL, 84 mmol) in CH_2Cl_2 (20 mL) was added dropwise at −78 °C to a solution of oxalylchloride (4 mL, 40 mmol) in CH_2Cl_2 (120 mL). After 30 min, a solution of alcohol **19** (4.7 g, 26 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the reaction mixture was stirred for 1 h. Finally, NEt_3 (16 mL, 127 mmol) was added, and the mixture was allowed to warm slowly to 0° C. After completion of the reaction (TLC control), water (100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude aldehyde was directly subjected to the following Wittig reaction:

*n*BuLi (15.2 mL, 38 mmol, 2.5 M in hexanes) was added dropwise at −78 °C to a vigorously stirred suspension of phosphonium salt **4**[12] (17.5 g, 38 mmol) and di-*tert*-butylphenol (1 g) in THF (150 mL). After 30 min, the reaction mixture was allowed to warm to 0 °C and additionally stirred for 1 h. Then a solution of the crude aldehyde (~26 mmol) in THF (20 mL) was added, and the reaction mixture was stirred overnight at room temperature. Finally, the solution was concentrated, and the residue was triturated with ether (6 × 150 mL). Concentration and purification by chromatography (cyclohexane/ethyl acetate 1:9, R_f = 0.23) gave a yellow oil. Yield: 6.2 g (21 mmol), 82 %; $[\alpha]_D^{20}$ = +67.0 (*c* = 0.8 in CH_2Cl_2). The *E/Z* isomer ratio was determined by comparison of the characteristic signals of the crude product **20**: *E/Z* = 4:1; *Z* isomer ***Z*-20**: 6.04 (dd, ^3J = 11 Hz, ^3J = 5 Hz, H-7); *E* isomer **20**: 6.18 (dd, ^3J = 16 Hz, ^3J = 6 Hz, H-7); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.26 (dd, ^3J = 15 Hz, ^3J = 10 Hz, 1 H; H-3), 6.52 (dd, ^3J = 15 Hz, ^3J = 10 Hz, 1 H; H-5), 6.22 (m, 1 H; H-4), 6.18 (dd, ^3J = 16 Hz, ^3J = 6 Hz, 1 H; H-7), 6.01 (m, 1 H; H-6), 5.93 (d, ^3J = 16 Hz, 1 H; H-2), 4.94 (m, 1 H; OCHO, THP), 4.32 (m, 1 H; H-9), 4.00 (m, 1 H; OCH, THP), 3.75 (s, 3 H; OMe), 3.50 (m, 1 H; OCH, THP), 2.63 (m, 1 H; H-8), 2.40 (t, ^3J = 7 Hz, 1 H; H-8), 2.32 (d, ^4J = 2 Hz, 1 H; H-11), 1.5–1.9 (m, 6 H); ^{13}C NMR

0947-6539/01/0715-3370 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15

($CDCl_3$, 125.5 MHz): $\delta = 167.5$ (quart. C, C=O, C(1)), 144.8 (CH, C(3)), 140.6 (CH, C(7)), 134.1 (CH, C(5)), 133.4 (CH, C(6)), 132.7 (CH, C(4)), 130.7 (CH, C(2)), 96.3 (CH, THP), 82.0 (quart. C, C(10)), 73,6 (CH, C(11)), 64.1 (CH_2, THP), 63.8 (CH, C(9)), 51.5 (CH_3, OMe), 39.1 (CH_2, C(8)), 30.9 (CH_2, THP), 25.3 (CH_2, THP), 19.8 (CH_2, THP); MS (EI, 70 eV): *m/z* (%): 290 (0.5) $[M]^+$, 270 (1)), 259 (0.8), 236 (0.5), 215 (0.8), 188 (67), 152 (20), 85 (100); HRMS-EI (70 eV) calcd for $C_{17}H_{22}O_4$: 290.1518, found: 290.1500.

Methyl(2*E*,4*E*,6*E*,9*S*)-9-hydroxy-2,4,6-undecatrien-10-ynoate (20b): Pyridinium *p*-toluene sulfonate (PPTS) (200 mg, 0.8 mmol) was added to a solution of THP ether **20** (5.3 g, 18 mmol) in MeOH (70 mL), and the solution was heated to 45 °C until TLC control indicated complete conversion. After cooling the solution, NEt_3 (0.5 mL) was added, and the solvents were removed under reduced pressure. Chromatography of the residue (cyclohexane/ethyl acetate 4:1, $R_f = 0.20$) gave a yellow oil. Yield: 3.3 g (16 mmol), 88 %; $[\alpha]_D^{20} = -16.6$ ($c = 0.7$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.26$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.52 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.20 (d, $^3J = 16$ Hz, 1H; H-7), 6.18 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-6), 5.93 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-4), 5.67 (d, $^3J = 16$ Hz, 1H; H-2), 4.30 (q, $^3J = 6$ Hz, 1H; H-9), 3.73 (s, 3H; OMe), 2.65 (m, 1H; H-8), 2.53 (t, $^3J = 7$ Hz, 1H; H-8), 2.33 (d, $^4J = 2$ Hz, 1H; H-11), 2.20 (brs, 1H; OH); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 167.6$ (quart. C, C(1)), 144.7 (CH, C(3)), 140.3 (CH, C(7)), 136.7 (CH, C(5)), 133.5 (CH, C(4)), 133.1 (CH, C(6)), 129.3 (CH, C(2)), 84.0 (quart. C, C(10)), 73.6 (CH, C(11)), 62.1 (CH, C(9)), 51.6 (CH_3, OMe), 41.0 (CH_2, C(8)); MS (EI, 70 eV): *m/z* (%): 206 (3) $[M]^+$, 185 (5), 168 (6), 140 (12), 135 (13), 113 (20), 97 (13), 85 (27), 75 (100), 59 (30), 57 (12); HRMS (70 eV) calcd for $C_{12}H_{14}O_3$: 206.0943, found: 206.0959.

Methyl(2*E*,4*E*,6*E*,9*S*)-9-hydroxy-11-iodo-2,4,6,10-undecatetraenoate (21): Bu_3SnH (1.3 mL, 4.7 mmol) was added dropwise at room temperature to a solution of alkyne **20b** (800 mg, 3.9 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in THF (20 mL). After 3 h, the reaction mixture was cooled to 0 °C, and iodine was added portionwise until a stable, slightly brown-violet colour persisted. Finally, after 20 min, the solution was diluted with CH_2Cl_2 (200 mL) and washed with saturated KF solution (2 × 30 mL) and saturated $Na_2S_2O_3$ solution (2 × 30 mL). The organic layer was dried over Na_2SO_4, concentrated and chromatographed with exclusion of light (cyclohexane/ethyl acetate 4:1, $R_f = 0.24$) to give a yellow oil. Yield: 886 mg (2.6 mmol), 68 %; $[\alpha]_D^{20} = -9.2$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 7.26 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.57 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-10), 6.52 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-5), 6.38 (d, $^3J = 16$ Hz, 1H; H-11), 6.25 (d, $^3J = 16$ Hz, $^3J = 7$ Hz, 1H; H-7), 6.23 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-6), 5.85 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-4), 5.83 (d, $^3J =$ 15 Hz, 1H; H-2), 4.17 (q, $^3J = 6$ Hz, 1H; H-9), 3.70 (s, 3H; OMe), 2.43 (m, 1H; H-8), 2.37 (q, $^3J = 6$ Hz, 1H; H-8), 2.10 (brs, 1H; OH); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 167.6$ (quart. C, C=O, C(1)), 147.5 (CH, C(3)), 144.7 (CH, C(10)), 140.3 (CH, C(7)), 133.9 (CH, C(5)), 133.1 (CH, C(6)), 129.0 (CH, C(4)), 120.3 (CH, C(2)), 77.9 (CH, C(11)), 73.6 (CH, C(9)), 51.6 (CH_3, OMe), 40.2 (CH_2, C(8)); MS (EI, 70 eV): *m/z* (%): 334 (1)) $[M]^+$, 303 (2), 257 (1), 233 (1), 183 (33), 152 (100), 120 (18), 91 (41), 59 (9); HRMS (70 eV) calcd for $C_{12}H_{15}IO_3$: 334.0064, found 334.0049.

Methyl(2*E*,4*E*,6*Z*,9*S*,10*E*,14*E*,16*E*,18*R*)-9-hydroxy-18-methyl-19-[(2,2,2-trifluoroacetyl)amino]-2,4,6,10,14,16-nonadecahexaen-12-ynoate (22): A solution of iodide **21** (700 mg, 2.1 mmol) in benzene (10 mL) and piperidine (1 mL) was degassed by bubbling argon through for 30 min. Then, $Pd(PhCN)_2Cl_2$ (20 mg, 0.05 mmol), a solution of alkyne **16** (642 mg, 2.6 mmol) in degassed benzene (7 mL) and CuI (40 mg, 0.2 mmol) were added sequentially. The reaction mixture was stirred for 2 h at room temperature and then diluted with ether (50 mL). After addition of saturated NH_4Cl solution (20 mL), the aqueous layer was separated and extracted with ether (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography (ether/pentane 2:1, $R_f = 0.36$) to afford a yellow oil. Yield: 796 mg (1.8 mmol), 87 %; $[\alpha]_D^{20} = -17.3$ ($c = 0.8$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.25$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.70 (dd, $^3J =$ 15 Hz, $^3J = 10$ Hz, 1H; H-15), 6.54 (m, 2H; H-5, NH), 6.50 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-14), 6.23 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-16), 6.18 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.06 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-10), 5.89 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-4), 5.69 (d, $^3J = 15$ Hz, 1H; H-11), 5.67 (d, $^3J = 16$ Hz, 1H; H-2), 5.65 (m, 1H; H-7), 5.45 (dd, $^3J = 16$ Hz, $^3J =$ 6 Hz, 1H; H-17), 4.31 (m, 1H; H-9), 3.82 (s, 3H; OMe), 3.05 (m, 1H; H-19), 2.85 (m, 1H; H-19), 2.65 (m, 1H; H-8), 2.53 (t, $^3J = 7$ Hz, 1H; H-8), 2.20 (m, 1H; H-18), 2.12 (brs, 1H; OH), 1.02 (d, $^3J = 7$ Hz, 3H; Me-18); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 167.2$ (quart. C, C=O, C(1)), 157.5 (q, $^3J = 39$ Hz, C=O, TFA), 144.7 (CH, C(3)), 141.9 (CH, C(17)), 140.3 (CH, C(7)), 138.1 (CH, C(15)), 136.7 (CH, C(5)), 135.5 (CH, C(4)), 135.3 (CH, C(10)), 133.1 (CH, C(11)), 132.4 (CH, C(6)), 130.4 (CH, C(16)), 129.3 (CH, C(2)), 117.9 (q, $J = 285$ Hz, quart. C, CF_3), 112.3 (CH, C(14)), 90.1 (quart. C, C(12)), 89.2 (quart. C, C(13)), 72.4 (CH, C(9)), 51.6 (CH_3, OMe), 44.8 (CH_2, C(19)), 41.1 (CH_2, C(8)), 37.1 (CH, C(18)), 17.3 (CH_3, Me-18); MS (EI, 70 eV): *m/z* (%): 437 (1) $[M]^+$, 419 (6), 268 (57), 173 (47), 152 (100), 145 (18), 120 (10), 91 (32), 69 (10); HRMS-EI (70 eV): calcd for $C_{23}H_{26}F_3NO_4$: 437.1813 found: 437.1786.

Methyl(2*E*,4*E*,6*Z*,9*S*,10*E*,12*Z*,14*E*,16*E*,18*R*)-9-hydroxyl-18-methyl-19-[(2,2,2-trifluoroacetyl)amino]-2,4,6,10,12,16-nonadecaheptaenoate (22b): A solution of alkyne **22** (233 mg, 0.5 mmol) in MeOH (5 mL) was added to a suspension of activated Zn (Cu/Ag)[15] in MeOH/water (1:1, 10 mL), and the reaction mixture was stirred overnight at room temperature. After dilution with MeOH (30 mL), the suspension was filtered through a pad of celite. Water (10 mL) and CH_2Cl_2 (50 mL) were added to the filtrate, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, and, after removal of the solvents in an air bath at room temperature under reduced pressure, the residue was purified by chromatography (ether/pentane 2:1, $R_f = 0.41$) to give a yellow oil. Yield: 121 mg (0.27 mmol), 55 %; $[\alpha]_D^{20} = -12.7$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.28$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.77 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-15), 6.62 (m, 2H; NH; H-5), 6.50 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-14), 6.27 (dd, $^3J = 15$ Hz, $^3J =$ 6 Hz, 1H; H-16), 6.23 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz 1H; H-6), 6.13 (dd, $^3J =$ 15 Hz, $^3J = 10$ Hz, 1H; H-10), 6.10 (dd, $^3J = 11$ Hz, $^3J = 10$ Hz, 1H; H-12), 5.86 (dd, $^3J = 11$ Hz, $^3J = 10$ Hz, 1H; H-13), 5.78 (d, $^3J = 15$ Hz, 1H; H-4), 5.68 (d, $^3J = 15$ Hz, 1H; H-2), 5.62 (m, 1H; H-11), 5.45 (dd, $^3J = 15$ Hz, $^3J =$ 7 Hz, 1H; H-7), 5.20 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-17), 4.20 (m, 1H; H-9), 3.82 (s, 3H; OCH_3), 3.05 (m, 1H; H-19), 2.85 (m, 1H; H-19), 2.40 (m, 2H; H-8), 2.20 (m, 1H; H-18), 1.02 (d, $^3J = 7$ Hz, 3H; Me-18); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 167.0$ (quart. C, C=O, C(1)), 157.1 (q, $^3J = 40$ Hz, C=O, TFA), 144.7 (CH, C(3)), 141.9 (CH, C(17)), 141.0 (CH, C(7)), 138.5 (CH, C(15)), 136.7 (CH, C(5)), 135.5 (CH, C(4)), 135.3 (CH, C(10)), 132.7 (CH, C(6)), 132.4 (CH, C(11)), 131.0 (CH, C(14)), 130.7 (CH, C(16)), 130.2 (CH, C(12)), 129.3 (CH, C(2)), 129.1 (C(13)), 118.0 (q, $J = 280$ Hz, quart. C, CF_3), 73.7 (CH, C(9)), 51.6 (CH_3, OMe), 44.8 (CH_2, C(19)), 41.1 (CH_2, C(8)), 37.1 (CH, C(18)), 17.3 (CH_3, Me-18); MS (EI, 70 eV): *m/z* (%): 439 (0.1) $[M]^+$, 422 (3), 378 (5), 317 (1), 284 (4), 269 (5), 192 (7), 152 (100), 136 (44), 105 (16); HRMS-EI (70 eV) calcd for $C_{23}H_{28}F_3NO_4$: 439.1970, found: 439.2001.

***tert*-Butyl *N*-[(2*R*,3E)-2-methyl-6-(1,1,1-trimethysilyl)-3-hexen-5-ynyl]-carbamate (28b)**: A solution of DMSO (5.6 mL, 77 mmol) in CH_2Cl_2 (10 mL) was added dropwise at −78 °C to a solution of oxalylchloride (3.5 mL, 39 mmol) in CH_2Cl_2 (120 mL). After 30 min, a solution of alcohol **28**[8] (4.2 g, 22 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and the reaction mixture was stirred for 1 h. Finally, NEt_3 (15 mL, 115 mmol) was added, and the mixture was allowed to warm slowly to 0 °C. After completion of the reaction (TLC control), water (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude aldehyde (4.1 g, 22 mmol) was directly subjected to the following Wittig reaction.

*n*BuLi (13.2 mL, 2.5 M in hexanes, 33 mmol) was added dropwise at −78 °C to a vigorously stirred suspension of phosphonium salt **9** (14.9 g, 33 mmol) in THF (150 mL). After 10 min, the reaction mixture was allowed to warm to −40 °C, was kept at this temperature for 30 min and was then cooled again to −78 °C. A solution of the crude aldehyde (5.7 mmol) in THF (15 mL) was then slowly added, and the reaction mixture was allowed to warm to room temperature overnight. After removal of the solvents under reduced pressure, the residue was triturated with diethyl ether (6 × 150 mL). The combined organic layers were evaporated to dryness, and the residue was purified by chromatography (cyclohexane/ethyl acetate 95:5, $R_f = 0.14$) to afford a pale yellow oil. Yield: 4.4 g (16 mmol), 72 %; $[\alpha]_D^{20} = +33.4$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.00$ (dd, $^3J = 15$ Hz, $^3J = 8$ Hz, 1H; H-3), 5.52 (d, $^3J = 15$ Hz, 1H; H-4), 4.57 (brs, 1H; NH), 3.02 (q, $^3J = 5$ Hz, 1H; H-1), 2.88 (quin, $^3J = 5$ Hz, 1H; H-1), 2.32 (t, $^3J = 7$ Hz, 1H; H-2), 1.33 (s, 9H; *t*Bu), 0.92 (d, $^3J = 7$ Hz, 3H;

Me-2), 0.16 (s, 9H; $SiMe_3$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 155.9$ (quart. C, C=O, Boc), 148.0 (CH, C(3)), 110.3 (CH, C(4)), 103.6 (quart. C, C(6)), 93.7 (quart. C, C(5)), 79.3 (quart. C, *t*Bu, Boc), 45.2 (CH_2, C(1)), 38.2 (CH, C(2)), 28.4 (CH_3, *t*Bu, Boc), 17.2 (CH_3, Me2), −0.08 (CH_3, $SiMe_3$); MS (EI, 70 eV): *m/z* (%): 281 (25) $[M]^+$, 225 (52), 224 (55), 210 (10), 208 (10), 181 (18), 166 (10), 152 (22), 102 (21), 72 (58), 57 (100); HRMS-EI (70 eV) calcd for $C_{15}H_{27}NO_2Si$: 281.1811, found: 281.1821.

***tert*-Butyl *N*-[(2*R*,3*E*)-2-methyl-3-hexen-5-ynyl]carbamate (29)**: K_2CO_3 (5 g) was added to a solution of TMS-acetylene **28b** (3.0 g, 14.3 mmol) in MeOH (80 mL), and the reaction mixture was stirred overnight at room temperature. After addition of water (50 mL), the solution was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvents under reduced pressure and filtration through a short plug of silica (cyclohexane/ethyl acetate 95:5, $R_f = 0.12$) afforded a slightly yellow oil. Yield: 2.8 g (13.2 mmol), 93%; $[\alpha]_D^{20} = +20.2$ ($c = 0.9$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 6.72$ (brs, 1H; NH), 6.00 (dd, $^3J = 15$ Hz, $^3J = 8$ Hz, 1H; H-3), 5.40 (d, $^3J = 15$ Hz, 1H; H-4), 3.06 (q, $^3J = 5$ Hz, 1H; H-1), 2.88 (m, 1H; H-1), 2.74 (d, $^2J = 2$ Hz, 1H; H-6), 2.36 (t, $^3J = 7$ Hz, 1H; H-2), 1.37 (s, 9H; *t*Bu), 0.92 (d, $^3J = 7$ Hz, 3H; Me-2); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 155.8$ (quart. C, C=O, Boc), 148.5 (CH, C(3)), 109.0 (CH, C(4)), 108.2 (CH, C(6)), 81.6 (quart. C, C(5)), 79.6 (quart. C, *t*Bu, Boc), 45.5 (CH_2, C(1)), 37.9 (CH, C(2)), 28.3 (CH_3, *t*Bu, Boc), 17.3 (CH_3, Me-2); MS (EI, 70 eV): *m/z* (%): 153 (30) $[M - t\text{Bu}+H]^+$, 126 (7), 92 (5), 80 (7), 79 (8), 77 (10), 59 (14), 57 (100), 41 (20); HRMS-EI (70 eV): calcd for $C_8H_{11}NO_2$ 153.0789, found: 153.0742.

***tert*-Butyl *N*-[(2*R*,3*E*,5*E*)-6-iodo-2-methyl-3,5-hexadienyl]carbamate (29b)**: $LiBEt_3H$ (2.4 mL, 1M in THF, 2.4 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (700 mg, 2.4 mmol) in THF (20 mL) at room temperature and under exclusion of light. After stirring the mixture for 1 h, alkyne **29** (250 mg, 1.2 mmol) in THF (5 mL) was added and stirring was continued for a further 2 h. Then the reaction mixture was cooled to 0 °C, and iodine was introduced portionwise until a slight brown colour persisted. After dilution with CH_2Cl_2 (200 mL) and washing with saturated $Na_2S_2O_3$ solution (2 × 20 mL), the organic layer was dried over Na_2SO_4. Removal of the solvents under reduced pressure and chromatography under light exclusion (cyclohexane/ethyl acetate 95:5, $R_f = 0.20$) gave a pale yellow oil. Yield: 303 mg (0.9 mmol) 75%; $[\alpha]_D^{20} = +22.4$ ($c = 1.1$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 6.95$ (dd, $^3J = 15$ Hz, $^3J = 11$ Hz, 1H; H-5), 6.21 (d, $^3J = 15$ Hz, 1H; H-6), 5.97 (dd, $^3J = 15$ Hz, $^3J = 11$ Hz, 1H; H-4), 5.52 (q, $^3J = 8$ Hz, 1H; H-3), 4.60 (brs, 1H; NH), 3.12 (m, 1H; H-1), 2.94 (m, 1H; H-1), 2.29 (t, $^3J = 7$ Hz, 1H; H-2), 1.39 (s, 9H; *t*Bu), 0.97 (d, $^3J = 7$ Hz, 3H; Me-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 155.9$ (quart. C, C=O, Boc), 145.1 (CH, C(5)), 138.2 (CH, C(3)), 130.4 (CH, C(4)), 79.2 (quart. C, *t*Bu, Boc), 77.7 (CH, C(6)), 45.7 (CH_2, C(1)), 37.4 (CH, C(2)), 28.4 (CH_3, *t*Bu, Boc), 18.0 (CH_3, Me-2); MS (EI, 70 eV): *m/z* (%): 337 (2) $[M]^+$, 281 (43), 264 (3), 220 (25), 207 (2), 154 (9), 93 (28), 57 (100); HRMS-EI (70 eV): calcd for $C_{12}H_{20}INO_2$: 337.0537, found.: 337.0549.

(2*R*,3*E*,5*E*)-6-Iodo-2-methyl-3,5-hexadien-1-amine (30): (Trimethylsilyl)-trifluoromethanesulfonate (TMSOTf) (0.4 mL, 2.2 mmol) was added to a solution of iodide **29b** (250 mg, 0.74 mmol) and 2,6-lutidine (0.32 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C and under light exclusion. The reaction mixture was allowed to warm to room temperature, was stirred for 1 h and was then quenched by addition of saturated NH_4Cl solution (5 mL) and saturated KF solution (5 mL). After the mixture had been stirred for 30 min, the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, concentrated and then filtered through a short plug of silica with ether as solvent to yield a brown oil: 157 mg, (0.66 mmol), 90%. The crude amine was directly subjected to the following amide coupling.

(2*E*,4*E*,6*E*,9*S*)-9-Hydroxy-11-iodo-2,4,6,10-undecatetraene acid (31): LiOH monohydrate (126 mg, 3 mmol) was added to a solution of ester **21** (230 mg, 0.7 mmol) in THF/MeOH/water (1:2:2, 10 mL), and the reaction mixture was stirred overnight under light exclusion. The pH of the solution was adjusted to 3 by addition of 10% NaH_2PO_4 solution, the then the solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was filtered through a short plug of silica. The crude acid **31**, yield: 172 mg (54 mmol), 78%, was directly subjected to the following amide coupling.

***N*1-[(2*R*,3*E*,5*E*)-6-Iodo-2-methyl-3,5-hexadienyl]-(2*E*,4*E*,6*E*,9*S*,10*E*)-9-hydroxy-11-iodo-2,4,6,10-undecatetraenamide (3)**: DEPC (0.11 mL, 0.8 mmol) and NEt_3 (0.15 mL, 0.9 mmol) were added to a solution of amine **30** (157 mg, 0.66 mmol) and acid **31** (224 mg, 0.70 mmol) in DMF (5 mL) under light exclusion and at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by chromatography under light exclusion (cyclohexane/ethyl acetate 1:1, $R_f = 0.53$) to afford a yellow oil. Yield: 263 mg (0.49 mmol), 74%; $[\alpha]_D^{20} = +5.3$ ($c = 0.7$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): $\delta =$ 7.26 (dd, $^3J = 15$ Hz, $^3J = 11$ Hz, 1H; H-3), 6.95 (dd, $^3J = 15$ Hz, $^3J = 11$ Hz, 1H; H-5′), 6.57 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-10), 6.52 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-5), 6.38 (d, $^3J = 16$ Hz, 1H; H-11), 6.25 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-7), 6.23 (dd, $^3J = 16$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.21 (d, $^3J =$ 15 Hz, 1H; H-6′), 5.97 (dd, $^3J = 15$ Hz, $^3J = 11$ Hz, 1H; H-4′), 5.82 (m, 1H; H-4), 5.52 (q, $^3J = 8$ Hz, 1H; H-3′), 5.50 (d, $^3J = 15$ Hz, 1H; H-2), 4.32 (brs, NH), 4.17 (q, $^3J = 6$ Hz, 1H; H-9), 3.41 (brs, 1H; OH), 3.30 (m, 1H; H-1′), 3.12 (m, 1H; H-1′), 2.43 (m, 2H; H-8), 2.31 (m, 1H; H-2′), 1.02 (d, $^3J =$ 7 Hz, 3H; Me-2′); ^{13}C NMR ($CDCl_3$, 125.6 MHz): $\delta = 166.1$ (quart. C, C=O, C(1)), 147.5 (CH, C(3)), 145.1 (CH, C(5′)), 144.9 (CH, C(10)), 139.4 (CH, C(7)), 137.9 (CH, C(3′)), 133.9 (CH, C(5)), 133.3 (CH, C(6)), 130.7 (CH, C(4′)), 129.3 (CH, C(4)), 120.4 (CH, C(2)), 78.2 (CH, C(11)), 77.7 (CH, C(6′)), 73.6 (CH, C(9)), 44.4 (CH_2, C(1′)), 39.6 (CH_2, C(8)), 37.7 (CH, C(2′)), 18.7 (CH_3, Me-2′); MS (EI, 70 eV): *m/z* (%): 538 (1) $[M]^+$, 491 (1), 411 (2), 357 (1), 303 (10), 254 (18), 220 (7), 183 (15), 127 (100), 91 (34), 43 (8); HRMS-EI (70 eV) calcd for $C_{18}H_{23}I_2NO_2$: 538.9816, found: 538.9835.

Ethyl(2*E*,4*E*,6*R*)-7-[(*tert*-butoxycarbonyl)amino]-6-methyl-2,4-heptadienoate (32): A solution of DMSO (1.1 mL, 15 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalylchloride (0.7 mL, 7 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 30 min, a solution of alcohol **28** (800 mg, 4.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise, and the reaction mixture was stirred for 1 h. Finally, NEt_3 (2.7 mL, 21 mmol) was added, and the mixture was allowed to warm slowly to 0 °C. After completion of the reaction (TLC control), 100 mL water was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude aldehyde (800 mg, 4.3 mmol) was directly subjected to the following Horner–Emmons reaction.

*n*BuLi (3.2 mL, 2.5M in hexanes, 8 mmol) was added dropwise to a solution of diisopropylamine (1.1 mL, 8 mmol) in THF (20 mL) at −78 °C. After 30 min at −78 °C, the solution was warmed to 0 °C for 10 min and then cooled again to −78 °C. This LDA solution was transferred dropwise to a solution of phosphonate **10** (1.8 g, 8 mmol) in THF (80 mL) at −78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to −30 °C for 30 min and was then cooled down to −78 °C again. The aldehyde (~4.3 mmol) in THF (10 mL) was added dropwise to this solution, and the mixture was allowed to warm to room temperature over 5 h. The solution was then diluted with ether (50 mL) and quenched by addition of saturated NH_4Cl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 150 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, $R_f = 0.42$) to afford a yellow oil. Yield: 1.0 g (3.6 mmol), 83%; $[\alpha]_D^{20} = +16.5$ ($c = 1.5$ in CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.08$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.05 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-4), 5.83 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5) 5.65 (d, $^3J = 15$ Hz, 1H; H-2), 4.90 (brs, 1H; NH), 4.03 (q, $^3J = 7$ Hz, 2H; OEt), 2.96 (m, 1H; H-7), 2.88 (m, 1H; H-7), 2.35 (m, 1H; H-6), 1.40 (s, 9H; *t*Bu), 1.26 (t, $^3J = 7$ Hz, 3H; OEt), 0.93 (d, $^3J = 7$ Hz, 3H; Me-2); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 166.9$ (quart. C, C=O, C(1)), 155.7 (quart. C, C=O, Boc), 146.1 (CH, C(3)), 144.3 (CH, C(5)), 128.0 (CH, C(4)), 119.9 (CH, C(2)), 78.7 (quart. C, *t*Bu, Boc), 59.9 (CH_2, OEt), 44.4 (CH_2, C(7)), 37.6 (CH, C(6)), 28.0 (CH_3, *t*Bu, Boc), 25.5 (CH_3, OEt), 16.9 (CH_3, Me-2); MS (EI, 70 eV): *m/z* (%): 227 (8) $[M\text{-}t\text{Bu}]^+$, 210 (6), 200 (9), 181 (3), 154 (47), 149 (73), 144 (40), 109 (35), 57 (100); HRMS-EI (70 eV) calcd for $C_{11}H_{17}NO_4$: 227.1157, found: 227.1149.

***tert*-Butyl*N*-[(2*R*,3*E*,5*E*)-7-hydroxy-2-methyl-3,5-heptadienyl]carbamate (32b)**: DIBAH (65 mL, 1M in hexanes, 65 mmol) was slowly added to a solution of ester **32** (7.3 g, 26 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was allowed to warm to −30 °C for 2 h and was then quenched by addition of MeOH (20 mL).

0947-6539/01/0715-3372 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15

Finally, after the mixture had been stirred for 1 h at room temperature, saturated Na-, K-tartrate solution (20 mL) was added, and the mixture was stirred until clarification of the phases. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, $R_f = 0.23$) to give a colourless oil. Yield: 5.6 g (23 mmol), 90%; $[\alpha]_D^{20} = +18.0$ ($c = 3.4$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.18$ (dd, $^3J = 15$ Hz, $^3J = 8$ Hz, 1H; H-5), 6.04 (dd, $^3J = 15$ Hz, $^3J = 8$ Hz, 1H; H-4), 5.76 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-6), 5.49 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-3), 4.62 (br s, 1H; NH), 4.12 (dd, $^3J = 6$ Hz, $^3J = 2$ Hz, 2H; H-7), 3.09 (q, $^3J = 6$ Hz, 1H; H-1), 2.93 (m, 1H; H-1), 2.33 (m, 1H; H-2), 2.15 (br s, 1H; OH), 1.40 (s, 9H; *t*Bu), 0.90 (d, $^3J = 7$ Hz, 3H; Me-2); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 156.0$ (quart. C, C=O, Boc), 137.3 (CH, C(3)), 131.2 (CH, C(5)), 130.9 (CH, C(6)), 129.8 (CH, C(4)), 79.2 (quart. C, *t*Bu), 63.1 (CH_2, C(7)), 46.0 (CH_2, C(1)), 37.4 (CH, C(2)), 28.4 (CH_3, *t*Bu), 17.0 (CH_3, Me-2); MS (EI, 70 eV): *m/z* (%): 241 (0.3) $[M]^+$, 185 (3), 184 (0.3), 168 (7), 167 (28), 149 (30), 110 (14), 109 (13), 94 (43), 57 (100), 41 (18); HRMS-EI (70 eV) calcd for $C_{13}H_{23}NO_3$: 241.1678, found: 241.1694.

(2*E*,4*E*,6*R*)-7-Amino-6-methyl-2,4-heptadien-1-ol (33): Trifluoroacetic acid (3 mL) was added to a solution of alcohol **32b** (336 mg, 1.4 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After completion of the reaction (TLC control), toluene (20 mL) was added, and all the solvents were removed under reduced pressure. The residue was taken up in MeOH (15 mL), then, after addition of K_2CO_3 (2 g), the mixture was stirred for 10 min and then diluted with water (10 mL) and CH_2Cl_2 (20 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (1×20 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvents under reduced pressure yielded the free amine as a yellow oil, 168 mg (1.2 mmol), 84%, which was directly subjected to the following amide coupling.

Methyl(2*E*,4*E*,6*E*)-8-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,4,6-octatrienoate (35): A solution of DMSO (12 mL, 165 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalylchloride (7.8 mL, 78 mmol) in CH_2Cl_2 (150 mL) at −78 °C. After 30 min, a solution of alcohol **34** (6 g, 41 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and the reaction mixture was stirred for 1 h. Finally, NEt_3 (25 mL, 200 mmol) was added, and the mixture was allowed to warm slowly to 0 °C. After completion of the reaction (TLC control), the reaction mixture was directly subjected to the following Wittig reaction.

*n*BuLi (24 mL, 2.5 M in hexanes, 60 mmol) was added dropwise to a vigorously stirred suspension of phosphonium salt **7**[12] (27.5 g, 60 mmol) and di-*tert*-butylphenol (1 g) in THF (150 mL) at −78 °C. After 30 min, the reaction mixture was allowed to warm to 0 °C and additionally stirred for 1 h. Then the crude Swern reaction mixture containing the aldehyde (~26 mmol) was added, and the suspension was stirred at room temperature overnight. Finally, the solution was concentrated, and the residue was triturated with diethyl ether (6×200 mL). Concentration and purification by chromatography (cyclohexane/ethyl acetate 9:1, $R_f = 0.42$) gave a yellow oil. Yield: 8.4 g (34 mmol), 85%; $[\alpha]_D^{20} = +5.3$ ($c = 2.5$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.25$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.55 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.28 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-4), 6.24 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-6), 6.20 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.86 (d, $^3J = 15$ Hz, 1H; H-2), 4.15 (dd, $^2J = 8$ Hz, $^3J = 6$ Hz, 1H; H-5′), 4.06 (dd, $^2J = 8$ Hz, $^3J = 6$ Hz, 1H; H-5′), 3.67 (s, 3H; OMe), 3.58 (dd, $^3J = 7$ Hz, $^3J = 2$ Hz, 1H; H-4), 2.20 (m, 2H; H-8), 1.44 (s, 3H; CMe), 1.40 (s, 3H; CMe); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta = 164.9$ (quart. C, C=O, C(1)), 142.1 (CH, C(3)), 137.9 (CH, C(7)), 131.8 (CH, C(5)), 129.8 (CH, C(4)), 126.3 (CH, C(6)), 117.7 (CH, C(2)), 106.6 (quart. C, C(2′)), 72.5 (CH, C(4′)), 66.3 (CH_2, C(5′)), 48.9 (CH_3, OMe), 34.7 (CH_2, C(8)), 24.3 (CH_3, CMe), 23.0 (CH_3, CMe); MS (EI, 70 eV): *m/z* (%): 252 (1) $[M]^+$, 237 (3), 149 (100), 109 (42), 101 (14), 93 (5), 79 (4); HRMS-EI (70 eV) calcd for $C_{14}H_{20}O_4$: 252.1361, found: 252.1352.

Methyl(2*E*,4*E*,6*E*,9*S*)-9,10-di[[1-(tert-butyl)-1,1-dimethylsilyl]oxy]-2,4,6-decatrienoate (35b): TosOH (1 g) was added to a solution of isopropylidene acetal **35** (8.4 g, 34 mmol) in MeOH (200 mL), and the solution was stirred at room temperature overnight. After addition of NEt_3 (1 mL), the solvent was removed under reduced pressure, and the residue was codistilled with toluene (3×100 mL). After addition of DMF (25 mL), imidazole (5.4 g, 80 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (11.3 g, 75 mmol), the reaction mixture was stirred at room temperature overnight and finally heated for 4 h to 45 °C. The solution was diluted with water (200 mL) and diethyl ether (500 mL), and the aqueous layer was separated and extracted with diethyl ether (1×200 mL). The combined organic layers were dried over Na_2SO_4, concentrated and the residue was purified by chromatography (cyclohexane/ethyl acetate 9:1, $R_f = 0.52$) to afford a yellow oil. Yield: 12.3 g (28 mmol), 82%; $[\alpha]_D^{20} = -1.5$ ($c = 0.8$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.26$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.57 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.28 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-4), 6.24 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-6), 6.20 (d, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.86 (d, $^3J = 15$ Hz, 1H; H-2), 3.73 (s, 3H; OMe), 3.69 (m, 1H; H-10), 3.53 (m, 1H; H-10), 3.42 (m, 1H; H-9), 2.34 (m, 1H; H-8), 2.20 (q, $^3J = 7$ Hz, 1H; H-8), 0.87 (s, 18H; 2 · Si*t*Bu), 0.05 (s, 12H; 2 · $SiMe_2$); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta = 167.6$ (quart. C, C=O, C(1)), 145.0 (CH, C(3)), 141.1 (CH, C(7)), 136.7 (CH, C(5)), 132.0 (CH, C(4)), 127.9 (CH, C(6)), 119.6 (CH, C(2)), 72.7 (CH, C(9)), 66.9 (CH_2, C(10)), 51.4 (CH_3, OMe), 25.8 (CH_3, Si*t*Bu), 18.3 (quart. C, Si*t*Bu), −4.4 (CH_3, SiMe), −5.4 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 440 (0.5) $[M]^+$, 384 (8), 383 (28), 308 (21), 289 (100), 277 (30), 251 (15), 215 (10), 183 (12), 151 (21), 149 (10), 147 (58), 117 (30), 57 (25); HRMS-EI (70 eV) calcd for $C_{23}H_{44}O_4Si_2$: 440.2778, found: 440.2760.

Methyl(2*E*,4*E*,6*E*,9*S*)-9-[[1-(tert-butyl)-1,1-dimethylsilyl]oxy]-2,4,6-decatrienoate (36): The HF · pyridine complex (2.1 mL, 70%, 72 mmol fluoride) was added to a mixture of pyridine (7.5 mL) and THF (40 mL), then this solution was added to a solution of DiTBS ether **35b** (10 g, 23 mmol) in pyridine (4.5 mL) and THF (30 mL). The reaction mixture was stirred for 20 h. After completion of the reaction (TLC control), the solution was diluted with diethyl ether (300 mL), washed with 0.5 M HCl (3×100 mL) and saturated $CuSO_4$ solution (1×100 mL) and then dried over Na_2SO_4. After removal of the solvents, the residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, $R_f = 0.34$) to afford a yellow oil. Yield: 5.4 g (16 mmol), 73%; $[\alpha]_D^{20} = +0.2$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.26$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.55 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.28 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-6), 6.24 (d, $^3J = 15$ Hz, 1H; H-4), 6.20 (d, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.86 (d, $^3J = 15$ Hz, 1H; H-2), 3.77 (m, 1H; H-9), 3.71 (s, 3H; OMe), 3.51 (m, 1H; H-10), 3.46 (m, 1H; H-10), 2.34 (m, 2H; H-8), 2.10 (br s, 1H; OH), 0.87 (s, 9H; Si*t*Bu), 0.05 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta =$ 167.5 (quart. C, C=O, C(1)), 144.8 (CH, C(3)), 140.7 (CH, C(7)), 135.4 (CH, C(5)), 132.3 (CH, C(4)), 128.5 (CH, C(6)), 120.0 (CH, C(2)), 72.3 (CH, C(9)), 66.0 (CH_2, C(10)), 51.5 (CH_3, OMe), 39.7 (CH_2, C(8)), 25.8 (CH_3, Si*t*Bu), 18.0 (quart. C, Si*t*Bu), −4.5 (CH_3, SiMe), −4.7 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 269 (11) $[M - t\text{Bu}]^+$, 217 (11), 175 (12), 131 (13), 117 (100), 75 (62), 59 (11), 57 (4); HRMS-EI (70 eV) calcd for $C_{13}H_{21}O_4Si$: 269.1209 found.: 269.1227.

Methyl(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-oxo-2,4,6,10-dodecatetraenoate (38): A solution of DMSO (4 mL, 55 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of oxalylchloride (2.6 mL, 29 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 30 min, a solution of alcohol **36** (3 g, 9.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and the reaction mixture was stirred for 1 h. Finally, NEt_3 (16 mL, 123 mmol) was added, and the mixture was allowed to warm slowly to 0 °C. After completion of the reaction (TLC control), formylmethylenetriphenyl-phosphonium chloride **37** (7.0 g, 20.4 mmol) was added, and the reaction mixture was stirred for 20 h at room temperature. Removal of the solvents, trituration with diethyl ether (6×100 mL) and purification by chromatography (cyclohexane/ethyl acetate 9:1, $R_f = 0.14$) afforded a bright yellow oil. Yield: 2.2 g (6.3 mmol), 70%; $[\alpha]_D^{20} = +14.2$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.56$ (d, $^3J = 8$ Hz, 1H; H-12), 7.28 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.76 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-10), 6.49 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.25–6.17 (m, 4H; H-11, H-4, H-6, H-7), 5.85 (d, $^3J = 14$ Hz, 1H; H-2), 4.47 (m, 1H; H-9), 3.73 (s, 3H; OMe), 2.54 (m, 2H; H-8), 0.89 (s, 9H; Si*t*Bu), 0.05 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta = 193.3$ (CH, C(12), 168.7 (quart. C, C=O, C(1)), 144.6 (CH, C(3)), 140.2 (CH, C(7)), 133.7 (CH, C(11)), 132.3 (CH, C(4)), 131.0 (CH, C(5)), 129.1 (CH, C(10)), 128.5 (CH, C(6)), 120.4 (CH, C(2)), 71.2 (CH, C(9)), 51.5 (CH_3, OMe), 40.9 (CH_2, C(8)), 25.7 (CH_3, Si*t*Bu), 18.1 (quart. C, Si*t*Bu), −4.6 (CH_3, SiMe), −4.7 (CH_3, SiMe).

Methyl(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-hydroxy-2,4,6,10-dodecatetraenoate (38b): A solution of aldehyde **38** (11.7 g, 34 mmol) in propan-2-ol (20 mL) was added to a solution of $CeCl_3 \cdot 7H_2O$

(12.6 g, 34 mmol) in propan-2-ol (200 mL). The mixture was cooled to 0 °C, and $NaBH_4$ (2.3 g, 60 mmol) was added portionwise to the solution under vigorous stirring. After 3 h, the reaction was quenched by cautious addition of iced water (150 mL) and was then extracted with diethyl ether (4 × 150 mL). The combined organic layers were dried over Na_2SO_4, the solvents were removed under reduced pressure, and the residue was purified by chromatography (cyclohexane/ethyl acetate 4:1, $R_f = 0.24$) to give a bright yellow oil. Yield: 9.1 g (26 mmol), 77 %; $[\alpha]_D^{20} = +6.5$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.28$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.51 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.17 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-4), 6.10 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-6), 5.90 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.82 (d, $^3J = 15$ Hz, 1H; H-2), 5.67 (m, 2H; H-11, H-10), 4.18 (m, 1H; H-9), 4.13 (d, $^3J = 5$ Hz, 2H; H-12), 3.72 (s, 3H; OMe), 2.42 (m, 1H; H-8), 2.32 (t, $^3J = 7$ Hz, 1H; H-8), 1.52 (br s, 1H; OH), 0.87 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta = 167.6$ (quart. C, C=O, C(1)), 144.9 (CH, C(3)), 140.9 (CH, C(7)), 136.0 (CH, C(5)), 134.0 (CH, C(11)), 132.1 (CH, C(4)), 129.0 (CH, C(10)), 128.3 (CH, C(6)), 119.8 (CH, C(2)), 72.2 (CH, C(9)), 62.9 (CH_2, C(12)), 51.5 (CH_3, OMe), 41.9 (CH_2, C(8)), 25.8 (CH_3, Si*t*Bu), 18.2 (quart. C, Si*t*Bu), −4.4 (CH_3, SiMe), −4.7 (CH_3, SiMe).

Methyl(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-(tetrahydroxy-2*H*-2-pyranyloxy)-2,4,6,10-dodecatetraenoate (38c): 3,5-Dihydro-2*H*-pyrane (DHP) (2.2 mL, 2.5 mmol) was added to a solution of allylic alcohol **38b** (1.7 g, 4.8 mmol) and PPTS (0.2 g, 0.8 mmol) in CH_2Cl_2 (100 mL), and the reaction mixture was stirred overnight. Then NEt_3 (1 mL) was added, and the solvent was removed under reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 9:1, $R_f = 0.28$) to give a yellow oil. Yield: 1.9 g (4.4 mmol), 93 %; $[\alpha]_D^{20} = +1.5$ ($c = 0.5$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.28$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.49 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.17 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-4), 6.13 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-6), 5.89 (d, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.81 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-2), 5.67 (m, 2H; H-10, H-11), 4.59 (d, $^3J = 3$ Hz, 1H; OCHO, THP), 4.17 (m, 1H; H-9), 3.98 (m, 1H; H-12), 3.83 (t, $^3J = 11$ Hz, 1H; H-12), 3.71 (s, 3H; OMe), 3.46 (m, 2H; OCH, THP), 2.43 (m, 1H; H-8), 2.31 (t, $^3J = 7$ Hz, 1H; H-8), 1.80 (m, 1H; THP), 1.72 (m, 1H; THP), 1.57 (m, 4H; THP), 0.85 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta = 167.5$ (quart. C, C=O, C(1)), 144.9 (CH, C(3)), 141.0 (CH, C(7)), 136.1 (CH, C(5)), 135.4 (CH, C(11)), 132.0 (CH, C(4)), 129.6 (CH, C(10)), 128.2 (CH, C(6)), 119.8 (CH, C(2)), 97.5 (CH, THP), 72.4 (CH, C(9)), 66.7 (CH_2, THP), 62.2 (CH_2, C(12)), 51.3 (CH_3, OMe), 41.9 (CH_2, C(8)), 30.6 (CH_2, THP), 25.8 (CH_3, Si*t*Bu), 25.4 (CH_2, THP), 19.5 (CH_2, THP), 18.2 (quart. C, Si*t*Bu), −4.4 (CH_3, SiMe), −4.7 (CH_3, SiMe).

(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-(tetrahydroxy-2*H*-2-pyranyloxy)-2,4,6,10-dodecatetraenic acid (39): LiOH monohydrate (143 mg, 3 mmol) was added to a solution of ester **38c** (532 mg, 1.2 mmol) in THF/MeOH/water (1:2:2, 10 mL), and the reaction mixture was stirred overnight. The pH of the solution was then adjusted to 4 by addition of 10 % NaH_2PO_4 solution, and the solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was filtered with diethyl ether through a short plug of silica. Yield: 368 g (0.87 mmol), 72 %. The crude acid was directly subjected to the following amide coupling.

***N*1-[(2*R*,3*E*,5*E*)-7-Hydroxy-2-methyl-3,5-heptadienyl]-(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-(tetrahydro-2*H*-2-pyranyloxy)-2,4,6,10-dodecatetraene amide (39b)**: BOP-Cl (446 mg, 1.8 mmol) and iPr_2NEt (0.35 mL, 2 mmol) were added to a solution of acid **39** (500 mg, 1.2 mmol)—which had been dried by repeated codistillation with toluene—in THF (10 mL), and the reaction mixture was stirred at room temperature. After 1.5 h, a solution of amine **33** (211 mg, 1.5 mmol) and DMAP (20 mg) in THF (3 mL) was added dropwise, and the reaction mixture was stirred overnight. Finally, the solvent was removed under reduced pressure, and the residue was directly purified by chromatography (cyclohexane/ethyl acetate 1:1, $R_f = 0.35$) to afford a yellow oil. Yield: 491 mg (0.9 mmol), 75 %; $[\alpha]_D^{20} = +16.3$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.21$ (dd, $^3J = 16$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.47 (dd, $^3J = 16$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.21 (dd, $^3J = 16$ Hz, $^3J = 9$ Hz, 1H; H-5′), 6.17 (dd, $^3J = 16$ Hz, $^3J = 9$ Hz, 1H; H-4), 6.12 (d, $^3J = 15$ Hz, 1H; H-6), 6.09 (d, $^3J = 15$ Hz, 1H; H-4′), 5.85 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-7), 5.80 (d, $^3J = 16$ Hz, 1H; H-2), 5.76 (dd, $^3J = 16$ Hz, $^3J = 10$ Hz, 1H , H-6′), 5.69 (m, 1H; H-10), 5.57 (q, $^3J = 8$ Hz, 1H; H-11), 5.50 (m, 1H; H-3′), 4.61 (q, $^3J = 3$ Hz, 1H; OCHO, THP), 4.20 (t, $^3J = 3$ Hz, 1H; H-9), 4.18 (m, 2H; H-7′), 3.98 (m, 1H; H-12), 3.85 (t, $^3J = 11$ Hz, 1H; H-12), 3.49 (m, 1H; OCH, THP), 3.41 (quin, $^3J = 6$ Hz, 1H; OCH, THP), 3.11 (m, 1H; H-1′), 2.94 (m, 1H; H-1′), 2.42 (m, 1H; H-8), 2.33 (m, 1H; H-2′), 2.31 (t, $^3J = 7$ Hz, 1H; H-8), 1.9 – 1.5 (m, 6H; THP), 1.01 (d, $^3J = 7$ Hz, 1H; Me-2′), 0.87 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 166.1$ (quart. C, C(1)), 141.1 (CH, C(3)), 139.7 (CH, C(7)), 137.3 (CH, C(3′)), 135.5 (CH, C(5)), 135.1 (CH, C(11)), 132.2 (CH, C(4)), 131.2 (CH, C(5′)), 131.1 (CH, C(6′)), 130.0 (CH, C(10)), 129.4 (CH, C(6)), 126.3 (CH,C(4′)), 122.8 (CH, C(2)), 97.6 (CH, THP), 72.4 (CH, C(9)), 66.8 (CH_2, THP), 63.3 (CH_2, C(7′)), 62.3 (CH_2, C(12)), 45.2 (CH_2, C(1′)), 42.0 (CH_2, C(8)), 37.2 (CH, C(2′)), 30.6 (CH, THP), 25.5 (CH_3, Si*t*Bu), 25.4 (CH_2, THP), 19.5 (CH_2, THP), 18.2 (quart. C, Si*t*Bu), 17.5 (CH_3, Me-2′), −4.3 (CH_3, SiMe), −4.7 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 488 (0.5) $[M - t\text{Bu}]^+$, 435 (0.4), 417 (0.4), 376 (1), 375 (3), 261 (2), 201 (12), 85 (100), 83 (4); HRMS-EI (70 eV) calcd for $C_{27}H_{42}NSiO_5$: 488.2823, found: 488.2855

***N*1-[(2*R*,3*E*,5*E*)-7-Hydroxy-2-methyl-3,5-heptadienyl]-(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-hydroxy-2,4,6,10-dodecatetraenamide (39c)**: PPTS (25 mg, 0.01 mmol) was added to a solution of THP ether **39b** (300 mg, 0.55 mmol) in propan-2-ol (50 mL), and the reaction mixture was heated to 55 °C. After completion of the reaction (4 – 5 h, TLC control), NEt_3 (0.25 mL) was added, the solvent was removed under reduced pressure, and the residue was purified by chromatography (cyclohexane/ethyl acetate 3:7, $R_f = 0.45$) to afford a brightly yellow oil. Yield: 184 mg (0.40 mmol), 73 %; $[\alpha]_D^{20} = +29.5$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.20$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.47 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.25 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-5′), 6.18 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-4), 6.14 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.10 (d, $^3J = 15$ Hz, 1H; H-6′), 6.04 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-4′), 5.87 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-7), 5.80 (d, $^3J = 15$ Hz, 1H; H-2), 5.75 (m, 1H; H-11), 5.68 (dd, $^3J = 15$ Hz, $^3J = 5$ Hz, 1H; H-10), 5.50 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-3′), 4.18 (q, $^3J = 6$ Hz, 1H; H-9), 4.15 (d, $^3J = 5$ Hz, 2H; H-12), 4.13 (dd, $^3J = 6$ Hz, $^3J = 2$ Hz, 2H; H-7′), 3.09 (q, $^3J = 6$ Hz, 1H; H-1′), 2.94 (m, 1H; H-1′), 2.42 (m, 1H; H-8), 2.33 (m, 1H; H-2′), 2.30 (t, $^3J = 7$ Hz, 1H; H-8), 1.8 – 1.5 (br m, 2H; OH), 1.02 (d, $^3J = 7$ Hz, 3H; Me-2′), 0.87 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 166.3$ (quart. C, C(1)), 141.0 (CH, C(3)), 139.6 (CH, C(7)), 137.1 (CH, C(3′)), 134.9 (CH, C(5)), 134.8 (CH, C(11)), 132.2 (CH, C(4)), 131.2 (CH, C(5′)), 129.9 (CH, C(4′)), 129.0 (CH, C(6)), 128.4 (CH, C(6′)), 127.3 (CH, C(10)), 123.0 (CH, C(2)), 72.3 (CH, C(9)), 63.0 (CH_2, C(7′)), 62.8 (CH_2, C(12)), 44.9 (CH_2, C(1′)), 42.0 (CH_2, C(8)), 37.1 (CH, C(2′)), 25.8, (CH_3, Si*t*Bu), 18.2 (quart. C, Si*t*Bu), 17.9 (CH_3, Me-2′), −4.4 (CH_3, SiMe), −4.8 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 404 (3) $[M - t\text{Bu}]^+$, 376 (3), 375 (11), 315 (14), 243 (7), 202 (14), 201 (100), 120 (15), 115 (8), 91 (14), 85 (15), 75 (47), 73 (63), 57 (6); HRMS-EI (70 eV) calcd for $C_{22}H_{37}NO_4Si$: 404.2257, found: 404.2231.

***N*1-[(2*R*,3*E*,5*E*)-2-Methyl-7-oxo-3,5-heptadienyl]-(2*E*,4*E*,6*E*,9*S*,10*E*)-9-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-12-oxo-2,4,6,10-dodecatetraenamide (40)**: nPr_4RuO_4 (10 mg, 0.03 mmol) was added to a suspension of diol **39c** (200 mg, 0.44 mmol) in 4-methylmorpholine *N*-oxide (150 mg, 1.2 mmol) freshly activated 3 Å molecular sieves (60 mg) in CH_2Cl_2 (5 mL), and the reaction mixture was stirred at room temperature. After 1 h, the aldehyde was directly purified by chromatography (cyclohexane/ethyl acetate 1:1, $R_f = 0.53$) to afford a lucent yellow oil. Yield: 157 mg (0.34 mmol), 78 %; $[\alpha]_D^{20} = +34.1$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.59$ (d, $^3J = 8$ Hz, 1H; H-7′), 9.53 (d, $^3J = 8$ Hz, 1H; H-12), 7.28 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 7.06 (dd, $^3J = 16$ Hz, $^3J = 10$ Hz, 1H; H-5′), 6.78 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-10), 6.46 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-5), 6.26 (dd, $^3J = 16$ Hz, $^3J = 10$ Hz, 1H; H-3′), 6.23 – 6.07 (m, 5H; H-11, H-6, H-4, H-6′, H-4′), 5.87 (dd, $^3J = 15$ Hz, $^3J = 7$ Hz, 1H; H-2), 5.80 (d, $^3J = 15$ Hz, 1H; H-2), 5.60 (br s 1H; NH), 4.47 (m, 1H; H-9), 3.42 (q, $^3J = 6$ Hz, 1H; H-1′), 3.28 (q, $^3J = 6$ Hz, 1H; H-1′), 2.55 (m, 1H; H-8), 2.43 (m, 1H; H-8), 2.31 (m, 1H; H-2′), 1.09 (d, $^3J = 7$ Hz, 3H; Me-2), 0.89 (s, 9H; Si*t*Bu), 0.04 (s, 3H; SiMe), 0.02 (s, 3H; SiMe); ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta =$ 193.8 (CH, C(7′)), 193.4 (CH, C(12)), 166.1 (quart. C, C(1)), 152.0 (CH, C(5′)), 148.6 (CH, C(4′)), 141.1 (CH, C(3)), 139.2 (CH, C(7)), 137.5 (CH, C(3′)), 133.9 (CH, C(11)), 132.5 (CH, C(4)), 130.9 (CH, C(5)), 129.0 (CH, C(10)), 128.7 (CH, C(6)), 123.0 (CH, C(2)), 120.2 (CH, C(6′)), 71.2 (CH, C(9)), 44.5 (CH_2, C(1′)), 40.9 (CH_2, C(8)), 37.9 (CH, C(2′)), 25.7 (CH_3,

0947-6539/01/0715-3374 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 15

Si*t*Bu), 18.1 (quart. C, Si*t*Bu), 17.4 (CH_3, Me-2′), −4.7 (CH_3, SiMe), −4.9 (CH_3, SiMe).

(9*S*,18*R*)-10-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-12,13-dihydroxy-18-methyl-20-aza-2*E*,4*E*,6*E*,12*E*,14*E*,16*E*-cycloicosahexaen-1-one (41): $VCl_3 \cdot (THF)_3$ (196 mg, 0.5 mmol) and then THF (60 mL) were added to zinc (20 mg, 0.3 mmol, < 60 μm, > 230 mesh ASTM) under strict exclusion of oxygen and moisture at the transfer. The mixture was then ultrasonicated until the solution changed from deep red to turquoise. Under vigorous stirring, a solution of dialdehyde **40** (100 mg, 0.2 mmol) in THF (20 mL) was added through a syringe pump over 12 h at room temperature. After an additional 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and saturated Na-,K-tartrate solution (20 mL) and stirred in air for 2 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by chromatography (cyclohexane/ethyl acetate 1:1, $R_f = 0.12$) to give a bright yellow oil. Yield: 55 mg (12 mmol), 60 %; $[\alpha]_D^{20} = +48.5$ ($c = 0.6$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.18$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.42 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.29 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-15), 6.18 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-4), 6.17 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.08 (d, $^3J = 15$ Hz, 1H; H-14), 6.02 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-16), 5.92 (d, $^3J = 15$ Hz, 1H; H-7), 5.84 (d, $^3J = 15$ Hz, 1H; H-2), 5.80 (m, 1H; NH), 5.71 (m, 1H; H-11), 5.68 (m, 1H; H-10), 5.51 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-17), 4.12 (m, 3H; H-12, H-13, H-9), 3.42 (m, 1H; H-19), 3.30 (m, 1H; H-8), 3.12 (q, $^3J = 6$ Hz, 1H; H-19), 2.42 (m, 1H; H-8), 2.31 (m, 1H; H-18), 1.5–1.8 (br m, 2H; OH), 1.02 (d, $^3J = 7$ Hz, 3H; Me-18), 0.85 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 166.2$ (quart. C, C(1)), 141.2 (CH, C(3)), 139.7 (CH, C(7)), 137.4 (CH, C(17)), 134.1 (CH, C(5)), 134.0 (CH, C(11)), 133.4 (CH, C(4)), 132.0 (CH, C(15)), 131.1 (CH, C(16)), 129.0 (CH, C(6)), 128.4 (CH, C(10)), 127.1 (CH, C(14)), 122.9 (CH, C(2)), 76.0 (CH, C(12)), 76.3 (CH, C(13)), 72.0 (CH, C(9)), 44.9 (CH_2, C(19)), 42.5 (CH_2, C(8)), 37.3 (CH, C(18)), 25.6, (CH_3, Si*t*Bu), 18.2 (quart. C, Si*t*Bu), 17.4 (CH_3, Me-18), −4.3 (CH_3, SiMe), −4.8 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 402 (5) $[M - t\text{Bu}]^+$, 368 (3), 329 (47), 277 (58), 215 (30), 202 (84), 201 (64), 135 (89), 95 (56), 75 (100); HRMS (70 eV) calcd for $C_{22}H_{32}NO_4Si$: 402.2100, found: 402.2081.

Derivatisation as triethylsilyl ether: A solution of triethylsilylchloride (7 μL, 0.04 mmol) in CH_2Cl_2 (0.1 mL) was added to a solution of pinacol **41** (5 mg, 0.01 mmol), NEt_3 (9 μL, 0.06 mmol) and DMAP (1 mg) in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After removal of the solvents, the residue was filtered through a short plug of silica with ether and then examined by mass spectroscopy. MS (EI, 70 eV): *m/z* (%): 687 (2) $[M]^+$, 402 (3), 373 (2), 315 (4), 277 (100), 201 (17), 199 (12), 121 (22), 75 (17); HRMS-EI (70 eV) calcd for $C_{38}H_{69}NO_4Si_3$: 687.4535, found: 687.4553.

(9*S*,18*R*)-9-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-18-methyl-12,13-(thioxomethylenedioxy)-20-aza-2*E*,4*E*,6*E*,10*E*,14*E*,16*E*-cycloicosahexaen-1-one (41b): A solution of thiophosgene (50 μL, 0.7 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a solution of pinacol **41** (150 mg, 0.32 mmol) and DMAP (146 mg, 1.2 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for 3 h and then quenched by the addition of 500 mg silica. After removal of the solvent, the residue was directly purified by chromatography ($CHCl_3$/MeOH 20:1, $R_f = 0.25$) to give a yellow oil. Yield: 104 mg (0.21 mmol), 65 %; $[\alpha]_D^{20} = +11.1$ ($c = 1$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.12$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.40 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.29 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-15), 6.18 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-4), 6.17 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.12 (d, $^3J = 15$ Hz, 1H; H-14), 6.02 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-16), 5.92 (d, $^3J = 15$ Hz, 1H; H-7), 5.80 (d, $^3J = 15$ Hz, 1H; H-2), 5.78 (m, 1H; H-11), 5.62 (m, 1H; H-10), 5.51 (dd, $^3J = 15$ Hz, $^3J = 4$ Hz, 1H; H-17), 5.44 (dd, $^3J = 7$ Hz, $^3J = 6$ Hz, 1H; H-12), 5.39 (dd, $^3J = 7$ Hz, $^3J = 4$ Hz, 1H; H-13), 4.10 (m, 1H; H-9), 3.30 (m, 1H; H-19), 3.12 (q, $^3J = 6$ Hz, 1H; H-8), 2.40 (m, 1H; H-19), 2.30 (m, 1H; H-8), 2.27 (m, 1H; H-18), 1.01 (d, $^3J = 7$ Hz, 3H; Me-18), 0.85 (s, 9H; Si*t*Bu), 0.02 (s, 6H; $SiMe_2$); ^{13}C NMR ($CDCl_3$, 125.5 MHz): $\delta = 183.2$ (quart. C, C=S), 166.0 (quart. C, C(1)), 141.0 (CH, C(3)), 138.7 (CH, C(7)), 137.9 (CH, C(17)), 134.2 (CH, C(5)), 134.0 (CH, C(11)), 133.7 (CH, C(4)), 132.1 (CH, C(15)), 130.5 (CH, C(16)), 129.7 (CH, C(6)), 128.0 (CH, C(10)), 127.1 (CH, C(14)), 122.4 (CH, C(2)), 83.1 (CH, C(12)), 82.7 (CH, C(13)), 73.2 (CH, C(9)), 44.9 (CH_2, C(19)), 41.5 (CH_2, C(8)), 37.1 (CH, C(18)), 25.1 (CH_3, Si*t*Bu), 18.2 (quart. C, Si*t*Bu), 17.6 (CH_3, Me-18), −4.1 (CH_3, SiMe), −4.6 (CH_3, SiMe); MS (EI, 70 eV): *m/z* (%): 501 (20) $[M]^+$, 444 (14), 363 (2), 292 (5), 228 (5), 135 (46), 75 (100); HRMS-EI (70 eV) calcd for $C_{27}H_{39}NO_4SiS$: 501.2369 found: 501.2350.

(9*S*,18*R*)-9-Hydroxy-18-methyl-12,13-(thioxomethylenedioxy)-20-aza-2*E*,4*E*,6*E*,10*E*,14*E*,16*E*-cycloicosahexaen-1-one (42): Acetic acid (120 μL, 2.1 mmol) and tetra-*n*-butylammonium fluoride (2 mL, 1M in THF, 2 mmol) were added to a solution of TBS-ether **41b** (70 mg, 0.14 mmol) in THF (0.5 mL). After being stirred for 2 d at room temperature under exclusion of light, the reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography ($CHCl_3$/MeOH 10:1, $R_f = 0.21$) to afford a yellow, glutinous oil. Yield: 18 mg (0.036 mmol), 26 %; $[\alpha]_D^{20} = +3.9$ ($c = 0.2$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.10$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.44 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.29 (m, 1H; H-15), 6.20 (dd, $^3J = 15$ Hz, $^3J = 9$ Hz, 1H; H-4), 6.19 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-6), 6.12 (d, $^3J = 15$ Hz, 1H; H-14), 6.02 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-16), 5.92 (d, $^3J = 15$ Hz, 1H; H-7), 5.80 (d, $^3J = 15$ Hz, 1H; H-2), 5.78 (m, 1H; H-11), 5.62 (m, 1H; H-10), 5.51 (m, 1H; H-17), 5.48 (m, 2H; H-12, H-13), 4.13 (m, 1H; H-9), 3.32 (m, 1H; H-19), 3.15 (q, $^3J = 6$ Hz, 1H; H-8), 2.45 (m, 1H; H-19), 2.34 (m, 1H; H-8), 2.20 (m, 1H; H-18), 1.02 (d, $^3J = 7$ Hz, 3H; Me-18); MS (EI, 70 eV): *m/z* (%): 387 (3) $[M]^+$, 367 (2), 279 (7), 263 (5), 220 (5), 205 (9), 167 (12), 120 (100), 85 (17), 76 (81); HRMS-EI (70 eV) calcd for $C_{21}H_{25}NO_4S$: 387.1504, found: 387.1540.

(9*S*,18*R*)-18-Methyl-20-aza-2*E*,4*E*,6*E*,10*E*,12*Z*,14*E*,16*E*-cycloicosaheptaen-1-one (1): 1,2,3-Trimethyldiazaphospholidine **43** (30 mg, 0.22 mmol) was added to a solution of thionocarbonate **42** (28 mg; 0.072 mmol) in ether (2 mL) at −20 °C under light exclusion. After 4 h, the reaction was quenched by addition of MeOH (0.1 mL), and the solvent was removed under reduced pressure. The residue was directly purified by preparative TLC ($CHCl_3$/MeOH 9:1, $R_f = 0.40$) to give a brown solid. Yield: 4.5 mg (0.014 mmol), 20 %; TLC: $R_f = 0.37$ (cyclohexane/ethyl acetate 1:1, $R_f = 0.14$ (ether); $[\alpha]_D^{20} = +60$ ($c = 0.01$ in DMF); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.20$ (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-3), 6.88 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-5), 6.52 (dd, $^3J = 15$ Hz, $^3J = 10$ Hz, 1H; H-15), 6.20 (m, 5H; H-4, H-12, H-13, H-14, H-16), 6.06 (m, 1H; H-6), 6.02 (m, 1H; H-7), 5.80 (m, 2H; H-10, H-11), 5.52 (dd, $^3J = 15$ Hz, $^3J = 6$ Hz, 1H; H-17), 5.41 (d, $^3J = 15$ Hz, 1H; H-2), 4.20 (m, 1H; H-9), 3.31 (m, 1H; H-19), 2.96 (m, 1H; H-19), 2.40 (m, 1H; H-8), 2.32 (m, 1H; H-18), 2.24 (m, 1H; H-8), 1.02 (d, $^3J = 7$ Hz, 3H; Me-18); MS (ESI, pos. mode, MeOH/$CHCl_3$ 2:1): 312 $[M+H]^+$; MS (ESI, neg. mode, MeOH/$CHCl_3$ 2:1): 345 $[M+Cl]^-$, 310 $[M-H]^-$.

Acknowledgements

This research was supported by the Bayer AG. We are grateful to Dr. B. Fugmann for samples of natural cyclamenol A.

[1] a) K. Ebnet, E. P. Kaldjian, A. O. Anderson, S. Shaw, *Annu. Rev. Immunol.* **1996**, *14*, 155–177; b) T. A. Springer, *Cell* **1994**, *76*, 301–314; c) T. A. Springer, *Nature* **1990**, *346*, 425–434.

[2] a) P. Sears, C.-H. Wong, *Angew. Chem.* **1999**, *111*, 2446–2471; *Angew. Chem. Int. Ed.* **1999**, *38*, 2300–2324; b) A. Giannis, *Angew. Chem.* **1994**, *106*, 188–191; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 178–181.

[3] For other natural products that inhibit leukocyte adhesion see: a) I. Kitagawa, T. Mahmud, K. Yokota, S. Nakagawa, T. Mayumi, *Chem. Pharm. Bull.* **1996**, *44*, 2009–2014; b) M. Kobayashi, M. Taifo, T. Hisashi, W. Wang, S. Aoki, *Chem. Pharm. Bull.* **1996**, *44*, 720–724.

[4] H. Müller, E. Bischoff, V. B. Fiedler, K. Weber, B. Fugmann, B. Rosen (Bayer AG), DE 4231289 A1 940324, **1994**; [*Chem. Abstr.* **1994**, *121*, 7441v].

[5] Part of this work was published in preliminary form: M. Nazaré, H. Waldmann, *Angew. Chem.* **2000**, *112*, 1171–1174; *Angew. Chem. Int. Ed.* **2000**, *39*, 1125–1128.

[6] Calculations were performed with HyperChem™, Version 5.02, Hypercube Inc., Gainsville, FL. USA.

[7] Examples for this type of isomerisation are: a) K. C. Nicolaou, S. E. Webber, J. Ramphal, Y. Abe, *Angew. Chem.* **1987**, *99*, 1077–1079; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1019–1021; b) M. B. Andrus,

S. D. Lepore, *J. Am. Chem. Soc.* **1997**, *119*, 2327 – 2328; c) B. Crousse, M. Alami, G. Linstrumenelle, *Tetrahedron Lett.* **1995**, *36*, 4245 – 4248.
[8] R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore, M. A. Tius, *J. Am. Chem. Soc.* **1995**, *117*, 2479 – 2490.
[9] K. C. Nicolaou, C. A. Veale, S. E. Webber, H. Katerinopoulos, *J. Am. Chem. Soc.* **1985**, *107*, 7515 – 7518.
[10] a) D. B. Collum, J. H. McDonald, W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 2117 – 2121; b) Y. Ohfune, M. Tomita, K. Nomoto, *J. Am. Chem. Soc.* **1981**, *103*, 2409 – 2410; c) K. C. Nicolaou, S. E. Webber, *J. Am. Chem. Soc.* **1984**, *106*, 5734 – 5736; d) L. C. Green, J. J. Kiddle, C. M. Thompson, *Tetrahedron Lett.* **1995**, *51*, 2865 – 2874.
[11] a) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521 – 522; b) S. Ohira, *Synth. Commun.* **1989**, *19*, 561 – 564; c) P. Callant, L. D'Haenens, M. Vandewalle, *Synth. Commun.* **1984**, *14*, 155 – 161.
[12] G. Durrant, R. H. Green, P. F. Lambeth, M. G. Lester, N. R. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1983**, 2211 – 2214.
[13] H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857 – 1867.
[14] a) M. Alami, B. Crousse, G. Linstrumelle, *Tetrahedron Lett.* **1994**, *35*, 3543 – 3544; b) M. Alami, S. Gueugnot, E. Domingues, G. Linstrumelle, *Tetrahedron Lett.* **1995**, *51*, 1209 – 1220; c) M. Avignon-Tropis, J. M. Berjeaud, J. R. Pougny, I. Fréchard-Ortuno, D. Guillerm, G. Linstrumelle, *J. Org. Chem.* **1992**, *57*, 651 – 654.
[15] W. Boland, S. Pantke, *J. Prakt. Chem.* **1994**, *336*, 714 – 715; b) W. Boland, N. Schroer, C. Sieler, M. Feigel, *Helv. Chim. Acta* **1987**, *70*, 1025 – 1040.
[16] A. Ehrlich, S. Rothemund, M. Brudel, M. Beyermann, L. A. Carpino, M. Bienert, *Tetrahedron Lett.* **1993**, *34*, 4781 – 4784.
[17] T. Mukaiyama, *Angew. Chem.* **1979**, *91*, 798 – 812; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707 – 721.
[18] a) W. J. Colucci, R. D. Tung, J. A. Petri, D. H. Rich, *J. Org. Chem.* **1990**, *55*, 2895 – 2903; b) J. Diago-Meseguer, A. L. Palomo-Coll, *Synthesis*, **1980**, *7*, 547 – 551.
[19] a) V. D. Mochel, D. F. Lawson, T. C. Farrar, *J. Am. Chem. Soc.* **1972**, *94*, 6203 – 6205; b) S. F. Brady, R. M. Freidinger, W. J. Paleveda, C. D. Colton, C. F. Homnick, W. L. Whitter, P. Curley, R. F. Nutt, D. F. Veber, *J. Org. Chem.* **1987**, *52*, 764 – 769.
[20] a) U. Schmidt, A. Kleefeldt, R. Mangold, *J. Chem. Soc. Chem. Commun.* **1992**, 1687 – 1689; b) T. Shioiri, Y. Yokoyama, Y. Kasai, S. Yamada, *Tetrahedron Lett.* **1976**, *32*, 2211 – 2217; c) S.-I. Yamada, Y. Kasai, T. Shioiri, *Tetrahedron Lett.* **1973**, *18*, 1595 – 1598.
[21] K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419 – 4420.
[22] B. H. Lipshutz, R. Keil, E. L. Ellsworth, *Tetrahedron Lett.* **1990**, *31*, 7257 – 7260.
[23] T. N. Mitchell, A. Amamria, H. Killing, D. Rutschow, *J. Organomet. Chem.* **1986**, *304*, 257 – 265.
[24] a) V. Farina, V. Krishnamurthy, W. J. Scott in *The Stille Reaction*, Wiley, Chichester, **1998**; b) V. Farina, B. Krishnan, D. R. Marshall, G. P. Roth, *J. Org. Chem.* **1993**, *58*, 5435 – 5444; c) E. Piers, R. W. Friesen, B. A. Keay, *Tetrahedron* **1991**, *47*, 4555 – 4570; d) J. E. Baldwin, R. M. Adlington, S. H. Ramcharitar, *Tetrahedron* **1992**, *48*, 2957 – 2976; e) A. Kalivretenos, J. K. Stille, L. H. Hegedus, *J. Org. Chem.* **1991**, *56*, 2883 – 2894.
[25] a) M. Barth, F. D. Bellamy, P. Renaut, S. Samreth, F. Schuber, *Tetrahedron* **1990**, *46*, 6731 – 6740; b) P. Mossett, P. Pointeau, F. Aubert, J. P. Lellouche, J. P. Beaucourt, R. Gree, *Bull. Soc. Chim. Fr.* **1990**, *127*, 298 – 315.
[26] a) L. A. Paquette, J. Dressel, P. D. Pansegrau, *Tetrahedron Lett.* **1987**, *28*, 4965 – 4968; b) K. Yamamoto, S. Kuroda, M. Shibutani, Y. Yoneyama, J. Ojima, S. Fujita, E. Ejiri, K. Yanagihara, *J. Chem. Soc. Perkin. Trans. 1* **1988**, 395 – 400; c) J. E. McMurry, J. G. Rico, Y. Shih, *Tetrahedron Lett.* **1989**, *30*, 1173 – 1176 and B. Jackson, G. Pattenden, *Tetrahedron Lett.* **1985**, *26*, 3393 – 3396; d) Y. Li, W. Li, Y. Li, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2953 – 2956; e) D. Ghiringhelli, *Tetrahedron Lett.* **1983**, *24*, 287 – 290; f) A. Ishida, T. Mukaiyama, *Chem. Lett.* **1976**, 1127 – 1130.
[27] a) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, *J. Org. Chem.* **1976**, *41*, 260 – 265; b) Y. Handa, J. Inanaga, *Tetrahedron Lett.* **1987**, *28*, 5717 – 5718; c) R. Schobert, *Angew. Chem.* **1988**, *100*, 869 – 871; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 855 – 857; d) T. A. Lipski, M. A. Hilfiker, S. G. Nelson, *J. Org. Chem.* **1997**, *62*, 4566 – 4567 and M. Kawatsura, F. Matsuda, H. Shirahama, *J. Org. Chem.* **1994**, *59*, 6900 – 6901.
[28] a) U. E. Udodong, B. Fraser-Reid, *J. Org. Chem.* **1988**, *53*, 2132 – 2134; b) J. L. Chiara, W. Cabri, S. Hanessian, *Tetrahedron Lett.* **1991**, *32*, 1125 – 1128; c) G. Butora, T. Hudlicky, S. P. Fearnley, M. R. Stabile, A. G. Gum, D. Gonzalez, *Synthesis* **1998**, *4*, 665 – 681.
[29] a) M. Kang, J. Park, A. W. Konradi, S. F. Pedersen, *J. Org. Chem.* **1996**, *61*, 5528 – 5531; b) A. G. Myers, P. S. Dragovich, *J. Am. Chem. Soc.* **1992**, *114*, 5859 – 5860; c) J.-M. Pons, J.-P. Zahra, M. Santelli, *Tetrahedron Lett.* **1981**, *22*, 3965 – 3968; d) Y. Kuwatani, I. Ueda, *Angew. Chem.* **1995**, *107*, 2017 – 2019; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1892 – 1894; e) L. Banfi, G. Guanti, A Basso, *Eur. J. Org. Chem.* **2000**, 939 – 946.
[30] a) E. J. Corey, P. B. Hopkins, *Tetrahedron Lett.* **1982**, *23*, 1979 – 1982; b) M. F. Semmelhack, J. Gallagher, *Tetrahedron Lett.* **1993**, *34*, 4121 – 4124.
[31] a) P. S. Manchand, P. S. Belica, M. J. Holman, T. Huang, H. Maehr, S. Y.-K. Tam, R. T. Yang, *J. Org. Chem.* **1992**, *57*, 3473 – 3478; b) I. Maeba, N. Morishita, P. Francom, M. J. Robins, *J. Org. Chem.* **1998**, *63*, 7539 – 7541; c) F. De Angelis, M. Marzi, P. Minetti, D. Misiti, S. Muck, *J. Org. Chem.* **1997**, *62*, 4159 – 4161; d) M. G. Lester, G. M. P. Giblin, G. G. A. Inglis, P. A. Procopiou, B. C. Ross, N. S. Watson, *Tetrahedron Lett.* **1993**, *34*, 4357 – 4360.
[32] G. Haufe, *J. Prakt. Chem.* **1996**, *338*, 99 – 113.
[33] A. G. M. Barrett, M. Pena, J. A. Willardsen, *J. Org. Chem.* **1996**, *61*, 1082 – 1100.
[34] M. Barth, F. D. Bellamy, P. Renaut, S. Samreth, F. Schuber, *Tetrahedron Lett.* **1990**, *46*, 6731 – 6740.

Received: February 9, 2001 [F3062]

  0947-6539/01/0715-3376 $ 17.50+.50/0