Stereoselective Total Synthesis of Reveromycin B and C19-*epi*-Reveromycin B

Keith E. Drouet and Emmanuel A. Theodorakis*[a]

Abstract: Our studies toward the total synthesis of the reveromycin family of natural products are described herein. Our synthetic approach is efficient, stereocontrolled, and convergent and has resulted in the first synthesis of reveromycin B (**4**) and C19-*epi*-reveromycin B (**55**). Key steps of this successful strategy include: a modified Negishi coupling (construction of C7 – C8 bond) and a Kishi – Nozaki reaction (construction of C19 – C20 bond), which were employed in the attachment of the target side chains. The key building blocks for the total synthesis were thus defined as vinyl iodide **6**, alkyne **7**, and alkyne **8**. Our synthesis illustrates the utility of the modified Negishi coupling for the construction of complex dienes, confirms the proposed stereochemistry of reveromycins and paves the way for the preparation of designed analogues for biological study.

Keywords: natural products · reveromycin · synthetic methods · total synthesis

Introduction

The reveromycins constitute a novel class of polyketide-type terrestrial metabolites of microbial origin. These natural products share common structural features comprised of an identical C1 – C24 backbone folded in such a way as to create a [6,6]- or [5,6]spiroketal core, flanked by two highly unsaturated side chains. The biological profile of these compounds is equally intriguing and includes a potent antiproliferative activity against certain human tumor cell lines. It has been postulated that the antitumor activity of these compounds stems from their interaction with the epidermal growth factor receptor (EGFR), whose intracellular signaling is essential for cellular proliferation. The combination of novel molecular architecture and interesting biological profile renders the reveromycins as attractive targets for chemical synthesis. Herein, we provide a detailed and updated account of our synthetic studies toward reveromycins, which culminated in the first total synthesis of reveromycin B (**4**) and C19-*epi*-reveromycin B (**55**).[1]

Background and biological relevance: Regulation of cellular proliferation is controlled by a number of mitogens, including a series of polypeptide growth factors.[2] Acting alone or synergistically these compounds can induce DNA synthesis and cellular reproduction. Undoubtedly, two of the best studied growth factors are the epidermal growth factor (EGF) and the transforming growth factor α (TGF-α), which exert their mode of action by binding to the extracellular part of the epidermal growth factor receptor (EGFR).[3] This binding induces conformational changes in the intracellular portion of EGFR, drastically affecting its tyrosine phosphorylation activities and thereby engaging the cell into the cell cycle.[4] Interestingly, many transformed cells overexpress EGFR and its ligands, an event known as autocrine secretion, which in turn prompts these cells to undergo continuous mitosis. For these reasons, the EGF receptor and its signal transduction pathways are considered prime targets for the development of new anticancer drugs.[5]

In an effort to discover new inhibitors of the EGF/TGF-α pathway, Osada and co-workers in Japan have isolated a new family of natural products constituted by reveromycin A (**1**), C (**2**), D (**3**), and B (**4**) (Figure 1).[6] These compounds were produced from the culture broth of an actinomycete strain of the genus *Streptomyces*, which was collected in Gunma Prefecture (Japan). Among all members of this family, reveromycin A (**1**) was the most naturally abundant component and consequently the one whose biological profile and chemical structure were most thoroughly studied.[7]

Biological studies revealed that reveromycins share a potent antiproliferative profile against certain human tumor cell lines at low micromolar concentrations.[7a] In addition, reveromycin A (**1**) was found to inhibit protein synthesis selectively in eukaryotic cells ($IC_{50} = 40$ nM) and induced morphological reversion of *src*^{ts}-NRK cells at $1.8\,\mu g\,mL^{-1}$ without any noticeable cytotoxicity. More recent in vivo

[a] Prof. Dr. E. A. Theodorakis, K. E. Drouet
University of California San Diego
Department of Chemistry & Biochemistry, Dept. 0358
9500 Gilman Drive, La Jolla, CA 92093-0358 (USA)
Fax: (+1) 858-822-0386
E-mail: etheodor@ucsd.edu

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

  0947-6539/00/0611-1987 $ 17.50+.50/0

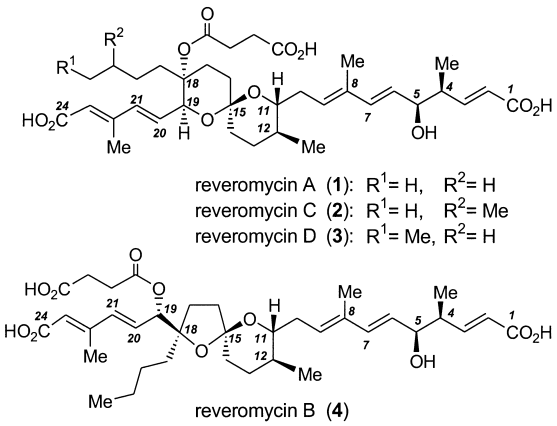


Figure 1. Structures of the reveromycin family of antibiotics.

studies in mice demonstrated that **1** exhibits strong antitumor activity against human ovarian carcinoma BG-1 cells, which are known to secrete large amounts of TGF-α.[7b] The observed antitumor effects of **1** were shown to be comparable to that of cisplatin treatment. Interestingly, however, the significant side effects that commonly result from cisplatin treatment, such as severe loss of body weight, were not observed with reveromycin A. The combination of the above data led to the proposition that reveromycins repress cell cycle progression at the G0-G1 checkpoint by interfering with transduction pathways associated with the EGF receptor.[2f, 7] Moreover, these studies revealed the potential of these natural products as tools for analyzing EGFR mediated cellular proliferation.[6, 7]

Following the interesting biological studies on reveromycin A (**1**), its chemical structure and absolute configuration were determined through a series of NMR experiments, degradation, and chemical correlation.[8, 9] These experiments unveiled a 1,7-dioxaspiro[5.5]undecane ([6,6]spiroketal) core adorned with a hemisuccinate ester, two alkenyl carboxylic acid side chains, and two alkyl groups. Of particular interest is the *trans*-diaxial orientation of the C18 succinate and C19 side chain which undoubtedly introduces strain on the spiroketal ring. The extreme scarcity of natural material precluded the independent structural elucidation of the other members of the reveromycin family. Nonetheless, their structures were reasonably deduced by spectroscopic comparison with that of **1** and revealed an identical C1 – C24 framework.

Results and Discussion

Retrosynthetic analysis: Close inspection of the proposed structures of reveromycin A (**1**) and B (**4**) indicated that their otherwise identical structures are formed by a different folding of the C1 – C24 backbone. Notably, the C18 oxygen atom that is succinylated in the structure of **1** participates in the formation of the [5,6]spiroketal core of **4** allowing the C19 oxygen to be succinylated. This observation formed the basis of our retrosynthetic analysis and defined alcohol **5** as a common and potentially biosynthetically relevant synthetic precursor of both reveromycin A and B (Figure 2). According to this plan, compound **5** could give rise to reveromycin B (**4**)

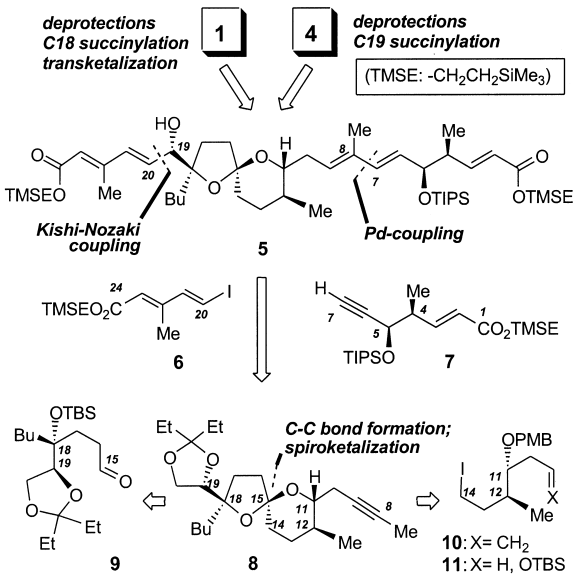


Figure 2. Retrosynthetic analysis of reveromycin A (**1**) and B (**4**).

after succinylation of the C19 hydroxyl group and functional group deprotection. Alternatively, the C19 alcohol of **5** could be recruited in a *trans*-spiroketalization reaction, thereby affording the [6,6]spiroketal ring system of **1** and ultimately leading to the synthesis of reveromycin A.[10]

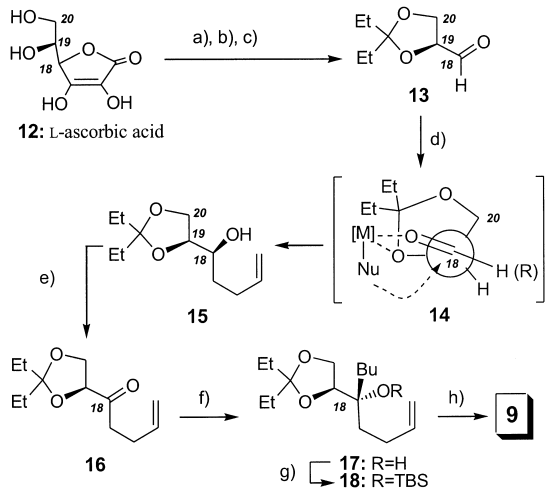
We also reasoned that the last step(s) of our synthesis should address the removal of all protecting groups, including deprotection of the C1 and C24 carboxylic acids and the C5 allylic alcohol. Since reveromycins are reported to be sensitive to basic treatment (facile desuccinylation),[6a] these deprotections needed to be performed under relatively neutral conditions and if possible in a single step. Consideration of the above factors led us to employ silicon-based protecting groups for both the carboxylic acids (TMSE: $Me_3SiCH_2CH_2$-)[11] and the C5 hydroxyl group (Figure 2).

Disassembly of compound **5** across the C7 – C8 and C19 – C20 bonds revealed three key components: vinyl iodide **6**, alkyne **7**, and alkyne **8** (Figure 2). In the synthetic direction, a palladium(0) coupling method was expected to be utilized for the union of intermediates **7** and **8**. Application of a Kishi – Nozaki coupling could then be used for the attachment of iodide **6** onto the main fragment. The latter coupling requires the presence of an aldehyde functionality at the C19 center, which was masked as an acetonide unit in compound **8**.[12] Further disconnection of alkyne **8** at the C15 carbon center unveils aldehyde **9** and iodide **10** (or iodide **11**) as putative synthetic precursors.

The above disconnections considerably reduced the level of complexity of the reveromycin framework and redefined our strategy as a problem in acyclic asymmetric synthesis. Our efforts toward the realization of this plan are described below.

Synthesis of core fragment 8: The synthesis of fragments **9**, **10**, and **11** are shown in Schemes 1, 2 and 3, while the assembly of the core fragment **8** is described in Scheme 4. Our synthetic venture towards aldehyde **9** began with conversion of L-ascorbic acid (**12**) to the known aldehyde **13** (Scheme 1). This was accomplished in 67% overall yield using a procedure reported in the literature.[13]

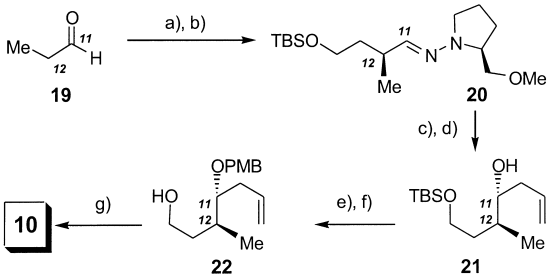
0947-6539/00/0611-1988 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11



Scheme 1. Synthesis of C15–C20 fragment **9**. a) 0.1 equiv Pd/C (10%), H_2, H_2O, 24 h, 55 °C, 96%; b) 1.3 equiv $Et_2C(OEt)_2$, 0.1 equiv CSA, DMF, 48 h, 25 °C, 82%; c) 1.2 equiv KIO_4, 2.0 equiv $KHCO_3$, THF/H_2O 1:1, 2 h, 23 °C, 85%; d) 1.5 equiv $H_2C{=}CHCH_2CH_2MgBr$ (2.0 M in THF), THF, −78 to 25 °C, 1 h, 92% (5:1 ratio at C18); e) 2.0 equiv PCC·celite, CH_2Cl_2, 25 °C, 2 h, 93%; f) 1.5 equiv BuMgBr (2.0 M in THF), THF, −78 °C, 1.5 h, 95% (4:1 ratio at C18); g) 1.3 equiv TBSOTf, 1.5 equiv 2,6-lutidine, CH_2Cl_2, 25 °C, 24 h, 99%; h) O_3, CH_2Cl_2, 20 min, −78 °C; 2.0 equiv Ph_3P, 95%.

Our plan was to convert the carbonyl center of **13** to the desired C18 tertiary alcohol of **9** using two sequential organometallic additions, which were predicted to proceed with good stereochemical control due to the chirality present on the C19 center (α-carbon) of **13**.[14] Recognizing that the desired chirality of the adduct could be controlled simply by altering the order of the carbanionic additions, we investigated the nature of the organometallic reagents simply on the basis of overall yield. Our studies led us to use Grignard reagents as the appropriate nucleophiles, since they gave better results than the corresponding organolithium counterparts. As shown in Scheme 1, reaction of 4-butene magnesium bromide with aldehyde **13** afforded alcohol **15** as a 5:1 mixture of diastereomers at the C18 center in 92% overall yield. This mixture was subsequently oxidized with PCC to the corresponding ketone **16** (93% yield). Treatment of **16** with butylmagnesium bromide afforded a 4:1 mixture of tertiary alcohols in 95% combined yield. The major diastereomer of this addition (alcohol **17**) was chromatographically isolated in 76% yield and was transformed to the desired aldehyde **9** upon silylation and ozonolysis (**17** → **18** → **9**, 94% overall yield). The stereochemical outcome of both Grignard additions was rationally explained through the intermediacy of a five-membered chelate formed by the C19 oxygen and the C18 carbonyl center (as shown for intermediate **14**).[15] Based on this chelation-controlled model, we expected that aldehyde **9** had the desired stereochemistry at the C18 center. However, additional and unambiguous confirmation of this structure remained at large until the entire fragment **8** was built (compound **8** was structurally confirmed using the transformations described in Scheme 5).

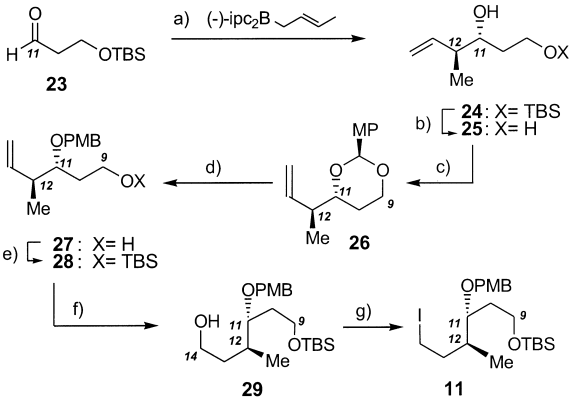
The synthesis of iodide **10** commenced with propionaldehyde (**19**) as illustrated in Scheme 2. Installation of the desired stereochemistry at the C12 and C11 centers was expected to occur via application of two enantioselective methods: Enders' SAMP hydrazone methodology[16] for alkylation α to a carbonyl group and Brown's homoallylboration.[17] To this end, condensation of **19** with SAMP hydrazine[18] afforded the corresponding hydrazone, which after deprotonation and alkylation furnished compound **20** in 64% overall yield. The enantiomeric excess of this addition was found to be greater than 95% as determined by NMR studies. Ozonolysis of **20** produced the labile aldehyde that was immediately treated with Brown's (+)-diisopinocampheylallylborane. Quenching of this mixture with basic hydrogen peroxide gave rise to the desired homoallyl alcohol **21** in 78% overall yield and excellent enantioselectivity ($ee > 95\%$). Protection of the resulting C11 hydroxyl group as the corresponding *p*-methoxybenzyl (PMB) ether, followed by fluoride-induced desilylation of the C14 silyl ether revealed primary alcohol **22** (81% yield over two steps). Alcohol **22** was converted to the desired iodide **10** in 97% yield upon treatment with triphenylphosphine, imidazole, and iodine[19] (Scheme 2).



Scheme 2. Synthesis of iodide **10**. a) 1.0 equiv SAMP (neat), 3.0 equiv **19**, 80 °C, 2 h, 92%; b) 1.1 equiv iPr_2NH, 1.1 equiv *n*BuLi (1.6 N in hexanes), THF, 0 °C, 6 h; 1.1 equiv *n*BuLi (1.6 N in hexanes), −20 °C, 2 h; 2.0 equiv $TBSO(CH_2)_2I$, −100 to −20 °C, 70%; c) O_3, CH_2Cl_2, −78 °C, 1 h; d) 1.5 equiv (+)-$(ipc)_2$B-$CH_2CH{=}CH_2$ (3 M in Et_2O), Et_2O, −78 °C, 2 h; 8.0 equiv H_2O_2 (30%), 13 equiv NaOH (3 N), −78 to 25 °C, 15 h, 78% (over two steps); e) 1.2 equiv KH, 1.5 equiv PMBCl, Et_2O, 0 °C, 6 h; f) 1.3 equiv TBAF·THF (1 M), THF, 25 °C, 1 h, 81% (over two steps); g) 2.4 equiv imidazole, 1.2 equiv Ph_3P, 1.2 equiv I_2, 0 °C, 1 h, 97%.

Although the above sequence delivered the C8–C14 fragment of the reveromycin framework and was used in the synthesis of the natural product[1] it suffered from the use of two chiral auxiliaries. During our repeated efforts to produce multigram amounts of advanced intermediates, we developed an expeditious synthesis of fragment **11**, during which only one chiral auxiliary was employed (Scheme 3). Thus, reaction of aldehyde **23** under Brown's asymmetric crotylboration protocol afforded alcohol **24** and introduced simultaneously both C11 and C12 chiral centers (80% yield).[20, 9b] Our initial attempts to benzylate the resulting C11 alcohol using *p*-methoxybenzyl chloride and a base (such as NaH, or KH) met with failure, since substantial amounts of by-products resulting from scrambling of the primary TBS group were observed. To circumvent this problem we desilylated compound **24** (using TBAF·THF in 98% yield) and treated the resulting diol **25** with *p*-methoxybenzyl dimethyl acetal under acid catalysis. This protocol furnished benzylidene acetal **26** in 98% yield. Exposure of **26** to DIBAL-H at −78 °C, followed by warming of the solution to 25 °C, resulted in a regioselec-

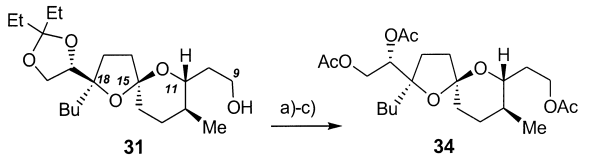
tive reductive cleavage of the acetal functionality and gave rise exclusively to primary alcohol **27** (91% yield).[21] Silylation of **27**, followed by hydroboration of the terminal olefin afforded, after quenching with hydrogen peroxide, compound **29** (82% overall yield). Treatment of the latter substance with triphenylphosphine, imidazole, and iodine produced the requisite fragment **11** in 96% yield (Scheme 3).



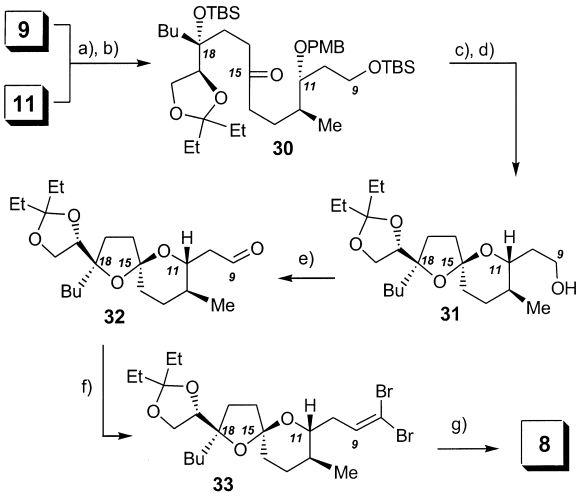
Scheme 3. Synthesis of iodide **11**. a) 1.5 equiv *t*BuOK, 1.6 equiv *trans*-2-butene, 1.5 equiv *n*BuLi, THF, −45 °C, 10 min, then 1.6 equiv (−)-ipc$_2$BOMe (1M in THF), 2.0 equiv $BF_3 \cdot Et_2O$, −78 °C, 1.0 equiv **23**, 3 h, then 3N NaOH, 30% H_2O_2, 25 °C, 18 h, 80%; b) 1.2 equiv TBAF · THF, THF, 25 °C, 30 min, 98%; c) 1.2 equiv $PMBCH(OMe)_2$, 0.1 equiv CSA, CH_2Cl_2, 25 °C, 6 h, 98%; d) 1.5 equiv DIBAL-H (1M in CH_2Cl_2), CH_2Cl_2, −78 to 25 °C, 2 h, 91%; e) 2.5 equiv imidazole, 1.3 equiv TBSCl, CH_2Cl_2, 25 °C, 1 h, 97%; f) 1.0 equiv $BH_3 \cdot THF$, −40 °C, 10 h, then 3N NaOH, 30% H_2O_2, 25 °C, 30 min, 85%; g) 2.4 equiv imidazole, 1.2 equiv Ph_3P, 1.2 equiv I_2, THF, 0 °C, 30 min, 96%.

The assembly of spiroketal fragment **8** by union of fragments **9** and **11** is described in Scheme 4. Treatment of iodide **11** with 2 molar equivalents of *tert*-butyllithium at −78 °C, followed by quenching of the carbanion with aldehyde **9** afforded a 1:1 mixture of diastereomeric alcohols at the C15 center, which upon Dess–Martin oxidation[22] produced ketone **30** (810% yield, over two steps). TBAF-induced simultaneous desilylation of the C18 and C9 hydroxyl groups, followed by reductive deprotection of the *p*-methoxybenzyl ether, resulted in the formation of spiroketal **31** as the sole product (87% overall yield). The C9 primary alcohol of **31** was then oxidized using Dess–Martin periodinane and the resulting aldehyde **32** was subjected to the modified Corey–Fuchs olefination procedure[23] to produce geminal dibromide **33**. Treatment of **33** with butyllithium and iodomethane afforded alkyne **8** (three steps, 85% starting from **30**).[24]

Before engaging further into the total synthesis of the target molecule, it was deemed necessary to confirm that spiroketal fragment **8** had the desired stereochemistry. To accomplish this objective, we sought to synthesize triacetate **34** and contrast its data with the comparable fragment obtained by degradation of the natural reveromycin A.[9a] Conversion of compound **31** to triacetate **34** was achieved in 74% yield using a sequence of steps that included: a) acetylation of the C9 hydroxyl group and b) CSA-induced deprotection of the C19–C20 acetonide and acetylation of the resulting diol (Scheme 5). As anticipated, compound **34** exhibited identical



Scheme 5. Structural verification of fragment **8**. a) 1.5 equiv Ac_2O, 3.0 equiv pyridine, CH_2Cl_2, 25 °C, 15 min; b) 0.1 equiv CSA, CH_2Cl_2/MeOH 9:1, 25 °C, 3 h; c) 3.0 equiv Ac_2O, 6.0 equiv Et_3N, CH_2Cl_2, 0 °C, 3 h, 74% (over three steps).



Scheme 4. Synthesis of C8–C20 fragment **8**. a) 1.0 equiv **11**, 2.1 equiv *t*BuLi, −78 °C, Et_2O, 0.5 h, then 1.4 equiv **9**, 0.5 h, 86%; b) 1.2 equiv Dess–Martin periodinane, CH_2Cl_2, 25 C, 1 h, 94%; c) 3.0 equiv TBAF · THF, THF, 50 °C, 2 h; d) H_2, 0.1 equiv Pd/C (10%), EtOH, 12 h, 25 °C, 80% (over two steps); e) 1.5 equiv Dess–Martin periodinane, CH_2Cl_2, 0 °C, 2 h, 94%; f) 5.0 equiv CBr_4, 10 equiv HMPT, THF, −30 °C, 30 min, 95%; g) 2.1 equiv *n*BuLi, THF, −78 to −20 °C, 20 min; 5.0 equiv MeI, THF, −78 to 0 °C, 2 h, 95%.

spectroscopic and analytical data with the one derived from degradation of the natural product. This observation confirmed unambiguously the previous prediction for the formation of the C18 stereocenter and further secured the stereochemical assignment for five out of the seven stereocenters of the reveromycin framework.

Synthesis of C1–C20 fragment 35: Having completed the synthesis of the core fragment **8** of the reveromycin skeleton, we set out to investigate methods for constructing the critical C7–C8 bond. To achieve this goal, we envisioned to employ a palladium(0) methodology and defined two different sets of coupling conditions: a Stille coupling between vinyl iodide **36** and vinyl stannane **37** and/or a Negishi coupling between vinyl zincate **38** and vinyl iodide **39** (Figure 3).[25] This plan offered the advantage of convergence, since both compounds **36** and **38** were expected to be produced by simple functionalization of fragment **8**, while compounds **37** and **39** could be furnished from fragment **40**. In the retrosynthetic direction, the desired stereochemistry at the C4 and C5 centers of **40** was foreseen to be introduced by implementation of Evans' aldol protocol.[26]

0947-6539/00/0611-1990 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

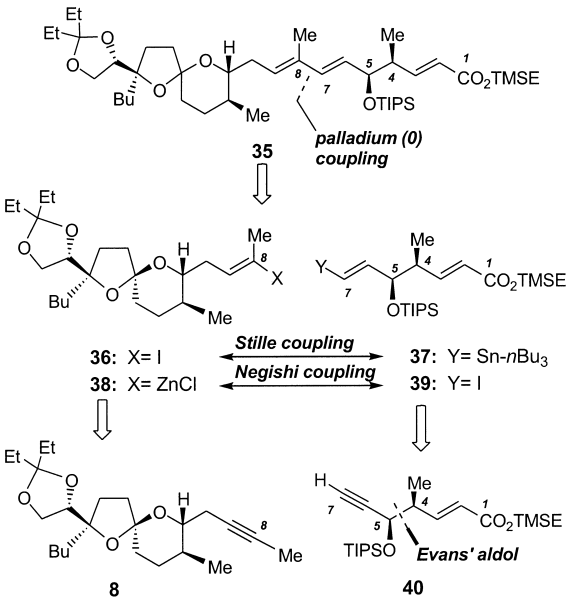
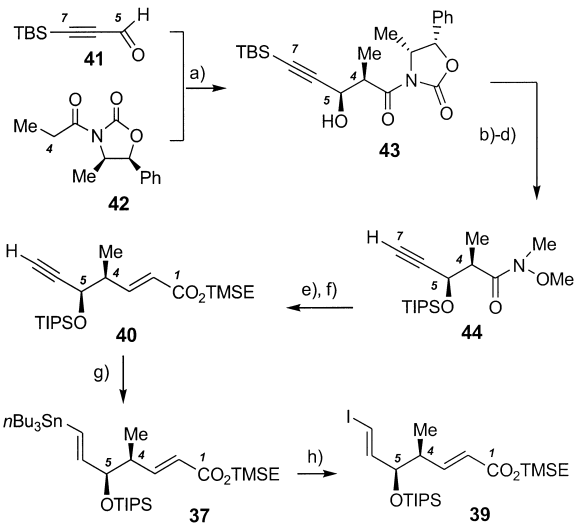


Figure 3. Strategies for the synthesis of C1–C20 fragment **35**.

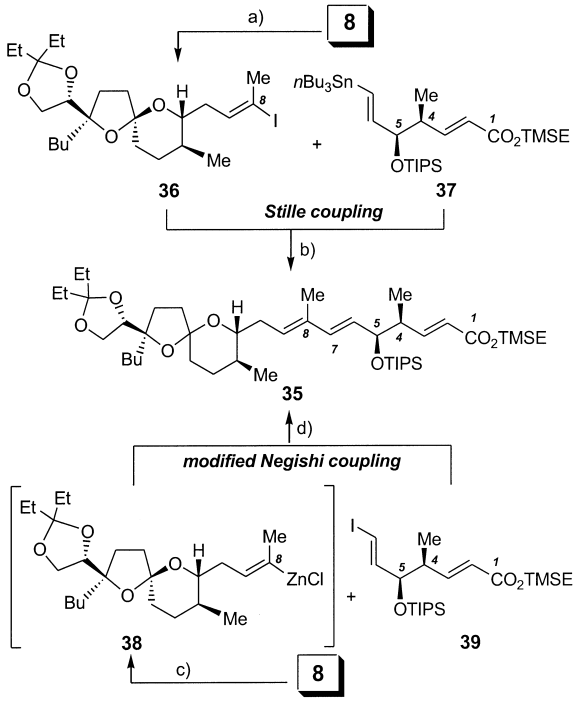
The synthesis of coupling partners **37** and **39** is described in Scheme 6 and commences with Evans coupling of aldehyde **41** with oxazolidinone **42**. This reaction afforded the desired



Scheme 6. Synthesis of C1–C7 fragments **37** and **39**. a) 1.0 equiv **42**, 1.0 equiv Bu_2BOTf, 1.2 equiv Et_3N, then 1.2 equiv **41**, CH_2Cl_2, -78 to $0\,^\circ C$, 5 h, 80%; b) 9.0 equiv $AlMe_3$, 9.0 equiv MeO-NHMe · HCl, THF, -30 to $0\,^\circ C$, 2 h; c) 2.0 equiv TBAF · SiO_2, THF, $25\,^\circ C$, 3 h; d) 1.5 equiv TIPSOTf, 3.0 equiv 2,6-lutidine, CH_2Cl_2, $25\,^\circ C$, 15 min, 81% (over three steps); e) 2.5 equiv DIBAL-H (1.5 M in toluene), THF $-78\,^\circ C$, 0.5 h; f) 2.5 equiv $Ph_3P{=}CH\text{-}CO_2TMSE$ (**45**), CH_2Cl_2, $25\,^\circ C$, 15 h, 91% (over two steps); g) 0.02 equiv $[Pd(PPh_3)_2Cl_2]$, 1.5 equiv n-Bu_3SnH, benzene, $5\,^\circ C$, 10 min, 91%; h) I_2, CH_2Cl_2, $0\,^\circ C$, 5 min, 90%.

aldol product **43** in 80% yield as the sole diastereomer and introduced the correct stereochemistry in the two remaining chiral centers of the reveromycin backbone. Treatment of **43** under the Weinreb conditions (Me_3Al and MeONHMe),[27] followed by fluoride-induced desilylation of the C7 center and silylation of the C5 propargylic alcohol furnished amide **44** in 81% overall yield. Exposure of **44** to DIBAL-H gave rise to the intermediate aldehyde, which without purification was treated with ylide **45** to afford ester **40** in 91% combined yield. Hydrostannylation of the terminal alkyne functionality of **40** under palladium(II) catalysis was expected to furnish the desired *trans*-vinyl stannane **37**.[28] Interestingly, the regiochemistry of this reaction was found to be dependent on the choice of solvents: An unseparable mixture of isomeric stannanes was obtained when THF or dichloromethane were employed as solvents, while in benzene this addition afforded exclusively the desired *trans*-adduct **37** in 91% yield. The putative Negishi coupling partner **39** was subsequently obtained by treatment of stannane **37** with iodine in dichloromethane (90% yield).[29]

With compounds **37** and **39** in hand, we focused our attention on the formation of the crucial C7–C8 bond (Scheme 7). In our initial studies we examined the potential



Scheme 7. Synthesis of C1–C20 fragment **35**. a) 1.0 equiv **8**, 2.0 equiv Cp_2ZrHCl, benzene, $25\,^\circ C$, 8 h; $I_2 \cdot CCl_4$ (excess), $0\,^\circ C$, 15 min, 53%; b) 1.0 equiv **36**, 1.0 equiv **37**, 0.05 equiv $[Pd(CH_3CN)_2Cl_2]$, DMF/THF 1:1, $25\,^\circ C$, 15 h, 52%; c) 1.0 equiv **8**, 2.0 equiv Cp_2ZrHCl, THF, $50\,^\circ C$, 2 h; 3.0 equiv $ZnCl_2$, THF, 5 min, $25\,^\circ C$; d) 1.0 equiv **38**, 1.1 equiv **39**, 0.05 equiv $[Pd(PPh_3)_4]$, THF, 2 h, $25\,^\circ C$, 84% over two steps.

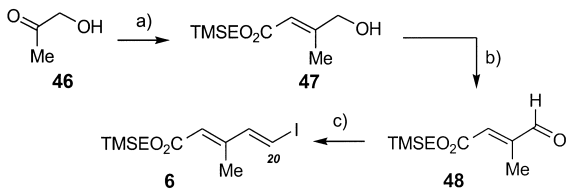
of a Stille coupling between iodide **36** and stannane **37**.[30] Compound **36** was expected to be synthesized by hydrozirconation of alkyne **8** and trapping of the intermediate vinyl zirconium species with iodine.[31] Unfortunately, this reaction was not regioselective and generated a mixture of vinyl iodides with a combined yield of 74%. The desired iodide **36** was produced in a 2.5:1 ratio, effectively reducing its overall yield to 53%. Undeterred by the low yield of **36**, we decided to attempt the Stille coupling before optimizing the above procedure. Nonetheless, coupling of **36** with stannane **37** under Stille conditions proved quite challenging.[32] Use of $[Pd(PPh_3)_4]$ as a catalyst afforded no coupled product, but

only compounds derived from dimerization of stannane **37**. The best results were produced using $[Pd(CH_3CN)_2Cl_2]$ as a catalyst and afforded the desired adduct **35**, albeit in low yield (52%).[30] The by-products of this reaction were identified as compounds arising from protodestannylation or dimerization of stannane **37**. Addition of excess iPr_2NEt (to buffer any adventitious acid)[33] and of copper(I) iodide (to accelerate the coupling)[34] proved ineffective. We briefly examined the effect of temperature: Although higher temperatures increased the rate of coupling process they did not increase the overall yield of **35** and cleaner conversion was observed at 25°C.

The low and often irreproducible yields of the above coupling were attributed to a combination of steric hindrance of trisubstituted vinyl iodide **36** and reduced electrophilicity due to the presence of the C8 methyl group. Both factors were held accountable for the attenuation of the rate of oxidative addition of **36** with palladium, opening the way for formation of by-products.

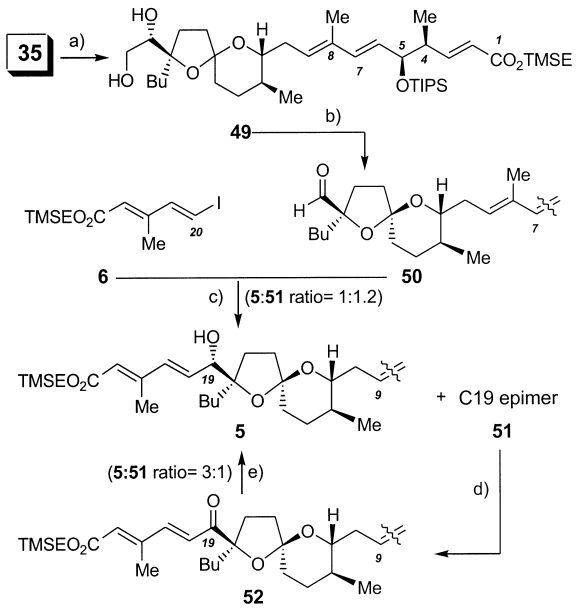
In considering this limitation we decided to alter the nucleophilic/electrophilic role of the above partners and evaluate the Negishi coupling (Scheme 7).[35, 36] We were particularly interested in studying a recent modification of the Negishi method, as reported by Panek and Hu.[37] The "modified" version of this coupling involves initial hydrozirconation of a methyl acetylene, followed by in situ transmetallation to the vinyl zincate (with $ZnCl_2$) and coupling with vinyl iodides using Pd^0 to afford the conjugated dienes in excellent yields. Much to our delight, this intricate reaction was facile and reproducible! A typical procedure involved treatment of alkyne **8** with two molar equivalents of Schwartz reagent at 50°C for two hours, followed by addition of 3 molar equivalents of $ZnCl_2$ (ca 1M in THF). The resulting mixture was treated with iodide **39** and catalytic amounts of $[Pd(PPh_3)_4]$ to produce the desired all-*trans* coupled product **35** in 84% yield. The overall efficiency of the Negishi coupling process was attributed to the good electrophilicity and steric accessibility of vinyl iodide **39** (facile oxidative addition) and good nucleophilicity of the vinyl zincate intermediate **38** (facile transmetallation). Moreover, the reported modification by Panek and Hu made the above reaction easier to perform. Our immediate success with the Negishi coupling led us to abandon any attempts to improve upon the yield of the Stille reaction.

Synthesis of C1–C24 fragment 5: Having completed the synthesis of fragment **35** we set out to prepare vinyl iodide **6**, our identified partner of the Kishi–Nozaki coupling (Scheme 8). Compound **6** was synthesized starting from commercially available acetol **46** which upon exposure to Wittig ylide **45** gave rise to ester **47** in 85% yield. PCC oxidation of the allylic hydroxyl group of **47** yielded aldehyde **48**, which upon treatment with $CrCl_2$ and CHI_3 produced exclusively the *trans*-iodide **6** in 57% overall yield.[38]



Scheme 8. Synthesis of iodide **6**. a) 1.0 equiv **46**, 1.2 equiv **45**, CH_2Cl_2, 25°C, 24 h, 85%; b) 2.1 equiv PCC·celite, CH_2Cl_2, 25°C, 2 h, 88%; c) 8.0 equiv $CrCl_2$, 2.5 equiv CHI_3, THF, 0 to 25°C, 0.5 h, 65%.

The construction of the C1–C24 reveromycin framework is described in Scheme 9. The required conversion of acetonide **35** to aldehyde **50** was achieved by initially transforming **35** to diol **49**. Among the several deprotection methods attempted, exposure of **28** to pyridinium *p*-toluenesulfonate (PPTS) in methanol at 40°C proved to be the best and resulted in the formation of diol **49** in 75% yield. Compound **49** was then oxidatively cleaved with $NaIO_4$ to afford aldehyde **50** (95% yield), thereby setting the stage for the crucial Kishi–Nozaki coupling.[39] This coupling was conducted in the presence of $CrCl_2$ and $NiCl_2$ (co-catalyst) and afforded a separable mixture of epimeric alcohols **5** and **51**. The structure of these alcohols was assigned on the basis of their NOE spectra (Figure 4). The two diastereomeric adducts **5** and **51** were obtained in a ratio of 1:1.2 and in 65% combined yield. Inexplicably, about 10–20% of starting aldehyde **50** remained unreacted even after further addition of reagents (catalysts and iodide **6**) and was recovered and reused after each



Scheme 9. Synthesis of C1–C24 fragment **5**. a) 3.0 equiv PPTS, MeOH, 3 h, 40°C, 75%; b) 6.0 equiv $NaIO_4$, THF/H_2O 2:1, 2 h, 0°C, 95%; c) 4.0 equiv **6**, 24 equiv $CrCl_2$ (with 0.5% $NiCl_2$), DMF, 25°C, 3 h, 65% (1.2:1 ratio at C19); d) 1.5 equiv Dess–Martin periodinane, CH_2Cl_2, 2 h, 25°C, 93%; e) 5.0 equiv $CeCl_3 \cdot 7H_2O$, 5.0 equiv $LiBH_4$ (2M in THF), THF/MeOH 1:1, −78 to 25°C, 3 h, 81%.

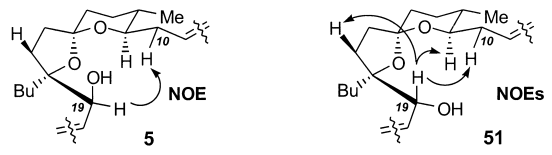


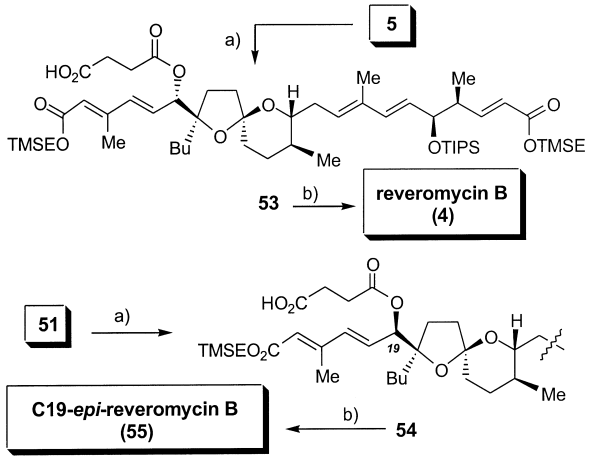
Figure 4. NOE data of the C19 proton for **5** and **51**.

0947-6539/00/0611-1992 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

coupling round. Furthermore, attempts to improve on the selectivity of this coupling by changing the temperature, the solvent or the composition of the catalysts proved unsuccessful. Nonetheless, it is particularly noteworthy that the intermediate organochromium nucleophile reacts selectively with a hindered neopentylic aldehyde, such as **50**, in the presence of other potent electrophilic centers.

In an attempt to increase the amount of desired adduct **5** we oxidized the unwanted epimer **51** to ketone **52** (93% yield), which upon Luche reduction[40] produced a 3:1 ratio of **5**:**51** in 81% combined yield (Scheme 9).

Synthesis of reveromycin B (4) and its C19 epimer (55): The last steps toward the synthesis of reveromycin B (**4**) are shown in Scheme 10. As expected, treatment of **5** with excess succinic



Scheme 10. Completion of the synthesis of reveromycin B (**4**) and C19-*epi* reveromycin B (**55**). a) 10 equiv succinic anhydride, 12 equiv DMAP, 25 °C, 3 h, 85% for **53**, 88% for **54**; b) 10 equiv TBAF · THF, THF, 2 h, 25 °C, 69% for **4**, 61% for **55**.

anhydride and DMAP afforded the succinate ester **53** in 85% yield. Much to our relief TBAF-induced a smooth removal of all protecting groups[41] and gave rise to synthetic reveromycin B (**4**) (59% yield, over two steps), which exhibited identical spectroscopic and analytical data with the natural product. Identical reaction conditions were also applied to alcohol **51** and produced C19 *epi*-reveromycin B (**55**) via ester **54** in 54% overall yield (over two steps).

Attempted synthesis of reveromycin A (1): Having achieved the synthesis of reveromycin B (**4**) we turned our attention to the construction of reveromycin A (**1**). We envisioned that an acid-catalyzed *trans*-spiroketalization reaction of **5** could produce the requisite [6,6]spiroketal system of **1**, as illustrated in Figure 5. To this end, a series of reagents and conditions were employed. PPTS had no effect, while prolonged treatment with camphorsulfonic acid (CSA) in $CHCl_3$ (or $CDCl_3$) gave rise to the formation of multiple by-products, presumably arising from elimination of the C5 silyl ether. Similar studies were performed with the entirely deprotected C1–C24 reveromycin framework. Unfortunately, we were unable

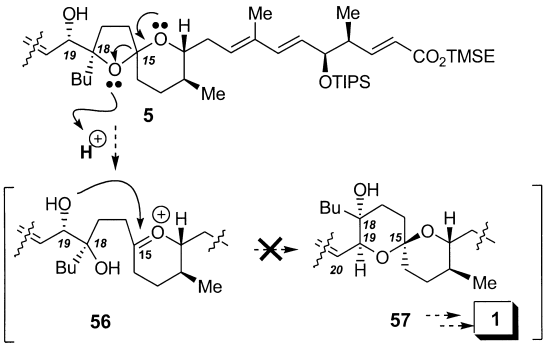


Figure 5. Attempted *trans*-spiroketalization strategy toward reveromycin A (**1**).

to observe the formation of [6,6]spiroketal core of reveromycin A under any circumstances.[42] It is conceivable that the desired *trans*-spiroketalization could be achieved by a suitable adjustment of protecting groups. Nonetheless, our failure to execute the desired transformation could also be attributed to the steric hindrance and energetic difference between the [5,6]- and [6,6]spiroketal core, in which the C18 tertiary hydroxyl group and C20–C24 side chain are axially oriented. These results parallel similar studies by McRae and Rizzacasa,[9b] who reported that an acid-catalyzed equilibration of the [5,6]- to [6,6]spiroketal ring of reveromycins favors strongly the [5,6]spiroketal ring of reveromycin B (**4**).

Conclusion

We have described herein a stereoselective total synthesis of (−) reveromycin B (**4**) and C19-*epi*-reveromycin B (**55**).[43] The successful synthetic route is highly efficient and convergent (four-component assembly) with the longest sequence numbering 21 steps (51 steps overall) and provides both reveromycin B (3.1% overall yield) and C19-*epi*-reveromycin B (2.8% overall yield). Highlights of our strategy include a modified Negishi coupling and a Kishi–Nozaki coupling, which were used for the installation of the polyene containing side chains of reveromycins. Moreover, a number of synthetic transformations on the spiroketal framework of reveromycins have been delineated and an improved synthesis of fragment **8** is presented herein. Our synthetic approach is amenable to the construction of novel and potentially bioactive analogues. Our synthesis also confirms the proposed stereochemistry of reveromycins.[44]

Experimental Section

General techniques: All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. All nonaqueous reactions were carried out using flame-dried glassware, under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone; dichloromethane (CH_2Cl_2) and toluene from calcium hydride; and benzene from potassium. *N*,*N*-Diisopropylethylamine, diisopropylamine, pyridine, triethylamine,

and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethyl sulfoxide and dimethylformamide were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4 Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel coated glass plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid, or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 and/or 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HR-MS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points (m.p.) are uncorrected, and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Alcohol 15: A solution of aldehyde **13** (15.0 g, 94.9 mmol) in tetrahydrofuran (200 mL) was cooled at $-78\,^\circ$C and treated with a 2 M solution of 4-magnesium bromobutene (71.1 mL, 142.2 mmol, prepared by adding magnesium turnings into a solution of 4-bromo-1-butene in tetrahydrofuran). After stirring at $-78\,^\circ$C for 15 min, the solution was allowed to warm to 0 °C and stirred at this temperature for 1 h. The reaction mixture was then cooled at $-78\,^\circ$C, quenched with aqueous saturated ammonium chloride (50 mL) and allowed to warm to 25 °C. The mixture was then diluted with Et_2O (300 mL) and the organic layer was washed with aqueous saturated sodium chloride (3 × 200 mL), collected, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by chromatography (0–15% Et_2O in hexanes) to afford alcohol **15** (18.7 g, 87.3 mmol, 92%) as a mixture of diastereomers (5:1 ratio at C18). **15**: colorless liquid; $R_f = 0.3$ (30% Et_2O in hexanes); $[\alpha]$: −45.1 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3464$, 2972, 2935, 2879, 1642, 1463, 1082, 915 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.85-5.80$ (m, 1H), 5.07 (dd, 1H, $J = 17.5$, 1.5 Hz), 4.98 (d, 1H, $J = 10.0$ Hz), 4.01–3.95 (m, 2H), 3.88–3.82 (m, 2H), 2.28–2.26 (m, 1H), 2.17–2.14 (m, 1H), 1.98 (br s, 1H), 1.69–1.60 (m, 4H), 1.55–1.53 (m, 1H), 1.45–1.43 (m, 1H), 0.93–0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 138.1$, 115.2, 112.8, 78.8, 70.2, 64.8, 31.7, 29.9, 29.4, 29.0, 8.1, 7.9; HR-MS: calcd for $C_{12}H_{22}O_3$ $[M+Cs]^+$ 347.0621, found 347.0640.

Ketone 16: A solution of alcohol **15** (11.0 g, 51.4 mmol) in CH_2Cl_2 (30 mL) was transferred under argon to a stirred suspension of pyridinium chlorochromate (22.1 g, 102.6 mmol, preabsorbed on celite) in CH_2Cl_2 (120 mL). After stirring for 2 h at 25 °C, the mixture was diluted with hexanes, filtered through a pad of celite, washed with Et_2O (2 × 50 mL), concentrated and subjected to flash chromatography (0–10% Et_2O in hexanes) to afford ketone **16** (10.3 g, 47.8 mmol, 93%). **16**: colorless liquid; $R_f = 0.45$ (20% Et_2O in hexanes); $[\alpha]_D^{25}$: −60.1 ($c = 1.8$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2966$, 2882, 1718, 1463, 1087, 916 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.82-5.78$ (m, 1H), 5.04 (dd, 1H, $J = 17.0$, 1.5 Hz), 4.98 (d, 1H, $J = 10.5$ Hz), 4.42 (t, 1H, $J = 8.0$ Hz), 4.19 (t, 1H, $J = 8.0$ Hz), 3.88 (dd, 1H, $J = 6.5$, 7.5 Hz), 2.72 (t, 2H, $J = 7.5$ Hz), 2.32 (q, 2H, $J = 8.0$ Hz), 1.72–1.61 (m, 4H), 0.94–0.84 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 209.8$, 137.0, 115.4, 115.0, 80.6, 66.5, 37.7, 29.1, 28.4, 26.8, 8.0, 7.9; HR-MS: calcd for $C_{12}H_{20}O_3$ $[M+Cs]^+$ 345.0464, found 345.0471.

Alcohol 17: A solution of ketone **16** (10.0 g, 47.1 mmol) in tetrahydrofuran (150 mL) was cooled at $-78\,^\circ$C and treated with butylmagnesium chloride (35.5 mL, 70.7 mmol, 2.0 M in tetrahydrofuran). After stirring for 1.5 h at $-78\,^\circ$C, the reaction mixture was treated with aqueous saturated ammonium chloride (50 mL), then allowed to warm to 25 °C and diluted with Et_2O (200 mL). The organic layers were washed with aqueous saturated ammonium chloride (2 × 200 mL), collected, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (0–10% Et_2O in hexanes) to afford alcohol **17** (9.67 g, 35.8 mmol, 76%), easily separated from its C18 epimer (2.41 g, 8.9 mmol, 19%). **17**: colorless liquid; $R_f = 0.45$ (20% Et_2O in hexanes); $[\alpha]_D^{25}$: +28.1 ($c = 1.25$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3483$, 2960, 2923, 2861, 1094, 835, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.84-5.76$ (m, 1H), 5.04 (dd, 1H, $J = 17.0$, 1.5 Hz), 4.96 (d, 1H, $J = 10.0$ Hz), 4.00 (t, 1H, $J = 6.5$, 9.0 Hz), 3.92 (t, 1H, $J = 8.0$ Hz), 3.83 (t, 1H, $J = 8.0$ Hz), 2.15–2.11 (m, 1H), 2.04–1.98 (m, 1H), 1.89 (br s, 1H), 1.67–1.48 (m, 6H), 1.47–1.42 (m, 1H), 1.38–1.26 (m, 5H), 0.94–0.86 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 138.6$, 114.6, 112.4, 79.9, 73.1, 64.8, 36.7, 33.3, 29.5, 29.1, 27.3, 25.7, 23.1, 14.0, 8.1, 8.0; HR-MS: calcd for $C_{16}H_{30}O_3$ $[M+Cs]^+$ 403.1247, found 403.1262.

Silyl ether 18: A solution of alcohol **17** (15.1 g, 55.8 mmol) in CH_2Cl_2 (60 mL) was treated at 25 °C with 2,6-lutidine (9.7 mL, 83.7 mmol), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (16.6 mL, 72.5 mmol). After stirring at 25 °C for 24 h, the mixture was diluted with Et_2O (100 mL), washed with aqueous saturated sodium chloride (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (0–10% Et_2O in hexanes) gave the silyl ether **18** (21.2 g, 55.2 mmol, 99%). **18**: colorless liquid; $R_f = 0.4$ (10% Et_2O in hexanes); $[\alpha]_D^{25}$: −47.4 ($c = 1.7$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2956$, 2853, 1462, 1252, 1083, 936, 773 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.88-5.78$ (m, 1H), 5.02 (d, 1H, $J = 17.0$ Hz), 4.95 (d, 1H, $J = 10.0$ Hz), 4.02 (dd, 1H, $J = 8.5$, 2.0 Hz), 3.90 (t, 1H, $J = 7.0$ Hz), 3.78 (t, 1H, $J = 7.0$ Hz), 2.10–2.00 (m, 2H), 1.70–1.59 (m, 6H), 1.42–1.40 (m, 6H), 0.91–0.87 (m, 18H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 139.2$, 114.1, 112.7, 80.8, 77.6, 65.6, 37.0, 35.7, 29.2, 28.2, 28.1, 25.9, 23.3, 18.6, 13.9, 8.3, 8.2, −2.1, −2.2; HR-MS: calcd for $C_{22}H_{44}O_3Si$ $[M - CH_3CH_2]^+$ 355.2668, found 355.2658.

Aldehyde 9: A solution of alkene **18** (12.0 g, 31.2 mmol) in CH_2Cl_2 (100 mL) was cooled at $-78\,^\circ$C and treated with ozone for 20 min. The excess ozone was then removed under a positive flow of argon, triphenylphosphine (16.4 g, 62.5 mmol) was added and the reaction mixture was allowed to warm to 25 °C over 1 h. The solution was concentrated and subjected to flash chromatography (0–10% Et_2O in hexanes) to afford aldehyde **6** (11.46 g, 29.69 mmol, 95%). **6**: colorless liquid; $R_f = 0.60$ (25% Et_2O in hexanes); $[\alpha]_D^{25}$: −3.1 ($c = 1.1$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2956$, 2858, 1728, 1462, 1252, 1082, 835, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.80$ (s, 1H), 4.05 (t, 1H, $J = 7.5$ Hz), 3.92 (t, 1H, $J = 7.5$ Hz) 3.75 (t, 1H, $J = 7.5$ Hz), 2.62–2.49 (m, 2H), 1.97–1.91 (m, 1H), 1.76–1.56 (m, 5H), 1.40–1.22 (m, 6H), 0.92–0.86 (m, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 202.5$, 113.2, 80.7, 77.2, 65.7, 38.7, 35.8, 29.1, 28.5, 27.9, 26.0, 25.9, 23.3, 18.5, 13.9, 8.3, 8.2, −2.2, −2.3; HR-MS: calcd for $C_{21}H_{42}O_4Si$ $[M+Cs]^+$ 519.1907, found 519.1929.

Hydrazone 20: A solution of diisopropylamine (10.7 g, 105.3 mmol) in tetrahydrofuran (300 mL) at 0 °C was treated with *n*-butyllithium (66 mL, 105.4 mmol, 1.6 M in hexane) added dropwise over a period of 0.5 h. The mixture was stirred at 0 °C for 20 min and treated with a solution of the SAMP hydrazone of propionaldehyde (**19**, 16.3 g, 95.8 mmol) in tetrahydrofuran (70 mL). The reaction was stirred at 0 °C for 6 h, then cooled to $-20\,^\circ$C and treated again with *n*-butyllithium (66 mL, 105.4 mmol, 1.6 M in hexane). After stirring at $-20\,^\circ$C for 2 h, the reaction mixture was cooled to $-110\,^\circ$C (liquid nitrogen/pentane bath) and treated with a solution of $TBSOCH_2CH_2I$ (54.8 g, 191.6 mmol) in tetrahydrofuran (50 mL). The mixture was allowed to warm slowly (over a period of 2 h) to $-20\,^\circ$C and the reaction was quenched with aqueous saturated ammonium chloride (200 mL). The reaction mixture was then warmed to 25 °C and the organic layer was diluted with Et_2O (500 mL), washed with aqueous saturated sodium chloride (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the crude residue (0–15% Et_2O in hexanes) afforded hydrazone **20** (22.0 g, 67.1 mmol, 70%). **20**: colorless liquid; $R_f = 0.55$ (30% Et_2O in hexanes); $[\alpha]_D^{25}$: −54.9 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2962$, 2925, 2857, 1473, 1264, 1097, 836, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.50$ (d, 1H, $J = 6.0$ Hz), 3.63 (m, 2H), 3.58 (dd, 1H, $J = 9.0$, 3.5 Hz), 3.49–3.39 (m, 1H), 3.37 (s, 3H), 3.35–3.32 (m, 1H), 2.66 (m, 1H), 2.40 (m, 1H), 1.92–1.50 (m, 7H), 1.05 (d, 3H, $J = 7.0$ Hz), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 143.6$, 74.7, 63.5, 61.2, 59.1, 50.3, 38.2, 33.7, 26.4, 25.9, 22.0, 19.0, 18.2, −5.41, −5.43; HR-MS: calcd for $C_{17}H_{36}N_2O_2Si$ $[M+Cs]^+$ 461.1599, found 461.1617.

Alcohol 21: A solution of hydrazone **20** (22.0 g, 67.1 mmol) in CH_2Cl_2 (250 mL) was cooled to $-78\,^\circ$C and treated with ozone until the starting material was consumed (tlc tests, ca 1 h depending on the scale). The mixture was then purged with oxygen (5 min) and argon (5 min), allowed to warm to 25 °C and concentrated. The crude aldehyde was taken immediately to the next step. A solution of (+)-methoxydiisopinocampheylborane (31.8 g, 100.6 mmol) in Et_2O (300 mL) was cooled to $-78\,^\circ$C and treated with allylmagnesium bromide (33 mL, 100.6 mmol, 3 M in Et_2O). After

0947-6539/00/0611-1994 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

stirring for 0.5 h at −78 °C, the mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was then cooled to −78 °C and treated with a solution of the crude aldehyde in Et_2O (30 mL). After stirring for 2 h at −78 °C, the reaction was treated with a solution of 30% hydrogen peroxide (95 mL) and 3N sodium hydroxide (432 mL) added dropwise over a period of 0.5 h. The mixture was then allowed to warm slowly to 25 °C and stirred at this temperature for 15 h. The organic layer was diluted with Et_2O (300 mL), washed with water (3 × 300 mL), dried over $MgSO_4$, filtered, concentrated, and purified by chromatography (0–10% Et_2O in hexanes) to afford alcohol **21** (13.5 g, 52.3 mmol, 78% over two steps). **21**: colorless liquid; $R_f = 0.4$ (20% Et_2O in hexanes); $[\alpha]_D^{25}$: −11.0 ($c = 1.1$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3485, 2960, 2924, 2861, 1090, 837, 780\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.91–5.82$ (m, 1H), 5.13–5.07 (m, 2H), 3.77–3.71 (m, 1H), 3.67–3.61 (m, 1H), 3.47–3.43 (m, 1H), 2.66 (br s, 1H), 2.34–2.28 (m, 1H), 2.24–2.12 (m, 1H), 1.77–1.51 (m, 3H), 0.94 (d, 3H, J = 7.0 Hz), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 135.5$, 117.1, 74.6, 61.1, 39.0, 36.0, 35.3, 26.0, 18.4, 16.4, −5.2; HR-MS: calcd for $C_{14}H_{30}O_2Si$ $[M+H]^+$ 259.2093, found 259.2104.

Alcohol 22: A solution of alcohol **21** (11.9 g, 46.4 mmol) in Et_2O (250 mL) was cooled to 0 °C and treated with potassium hydride (2.2 g, 55.7 mmol, washed with Et_2O) followed by 4-methoxybenzyl chloride (10.9 g, 69.7 mmol). After stirring for 6 h, the reaction was cooled to −30 °C and quenched with ice/water added cautiously. The mixture was then diluted with Et_2O (100 mL) and allowed to warm to 25 °C. The organic layer was washed with aqueous saturated sodium chloride (3 × 200 mL), collected, dried ($MgSO_4$), filtered through a short pad of silica, and concentrated. The crude residue was dissolved in Et_2O (50 mL) and treated with *tert*-butylammonium fluoride (56 mL, 56 mmol, 1M in THF) for 0.5 h at 25 °C. Aqueous saturated ammonium chloride (200 mL) was then added and the organic layer was extracted with Et_2O (3 × 200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (40–60% Et_2O in hexanes) to afford alcohol **22** (9.93 g, 37.6 mmol, 81% yield over two steps). **22**: colorless liquid; $R_f = 0.4$ (70% Et_2O in hexanes); $[\alpha]_D^{25}$: −11.3 ($c = 1.49$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3408, 2934, 1612, 1513, 1247, 1060, 821\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.27$ (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.5 Hz), 5.88–5.80 (m, 1H), 5.12 (d, 1H, J = 17.0 Hz), 5.07 (d, 1H, J = 10.5 Hz), 4.55 (d, 1H, J = 10.5 Hz), 4.41 (d, 1H, J = 11.0 Hz), 3.80 (s, 3H), 3.78–3.60 (m, 2H), 3.30–3.28 (m, 1H), 2.35 (t, 2H, J = 6.5 Hz), 1.90–1.50 (m, 4H), 0.94 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.3$, 135.3, 130.6, 129.5, 116.8, 113.8, 82.5, 71.4, 60.4, 55.2, 35.2, 35.0, 32.8, 15.8; HR-MS: calcd for $C_{16}H_{24}O_3$ $[M+H]^+$ 265.1804, found 265.1816.

Iodide 10: Imidazole (4.36 g, 64.12 mmol) followed by triphenylphosphine (8.40 g, 32.06 mmol) was added to a solution of alcohol **22** (7.05 g, 26.66 mmol) in THF (120 mL) and the mixture was stirred at 0 °C for 10 min. The flask was then protected from the light with aluminum foil and the mixture was treated with iodine (8.14 g, 32.06 mmol) introduced slowly (over 5 min). After stirring at 0 to 25 °C for 30 min, the reaction mixture was diluted with Et_2O (200 mL) and washed with aqueous saturated sodium thiosulfate (2 × 100 mL) and aqueous saturated sodium bicarbonate (2 × 100 mL). The organic layer was dried ($MgSO_4$), concentrated, and subjected to flash chromatography (0–10% Et_2O in hexanes) to yield iodide **10** (9.67 g, 25.85 mmol, 97%). **10**: colorless liquid; $R_f = 0.7$ (10% Et_2O in hexanes); $[\alpha]_D^{25}$: −7.8 ($c = 1.3$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2936, 2852, 1614, 1510, 1249, 1181, 1097, 1040, 825\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.26$ (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J = 8.0 Hz), 5.85–5.80 (m, 1H), 5.11 (d, 1H, J = 17 Hz), 5.07 (d, 1H, J = 10 Hz), 4.50 (d, 1H, J = 10 Hz), 4.43 (d, 1H, J = 10 Hz), 3.80 (s, 3H), 3.31–3.20 (m, 2H), 3.14–3.1 (m, 1H), 2.3–2.2 (m, 2H), 2.1–2.0 (m, 1H), 1.9–1.8 (m, 1H), 1.7–1.6 (m, 1H), 0.90 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.2$, 135.5, 130.8, 129.3, 116.9, 113.7, 81.7, 80.8, 71.2, 55.2, 36.7, 36.3, 35.2, 14.6; HR-MS: calcd for $C_{16}H_{23}IO_2$ $[M+Cs]^+$ 506.9797, found 506.9817.

Alcohol 24: A suspension of potassium *tert*-butoxide (13.4 g, 119.5 mmol) and *trans*-2-butene (12 mL, 127.5 mmol) in THF (50 mL), was mechanically stirred, cooled to −45 °C and treated with *n*-BuLi (48 mL, 119.5 mmol, 2.5M in hexanes) added over a period of 10 min. The mixture was cooled to −78 °C and treated with a solution of (−)-methoxydiisopinocampheylborane (40.3 g, 127.5 mmol) in THF (125 mL). The reaction mixture was stirred for 30 min and treated with $BF_3 \cdot OEt_2$ (19.9 mL, 159.3 mmol) followed by addition of aldehyde **23** (15.0 g, 79.7 mmol). After 3 h, the reaction was quenched with 3N NaOH (270 mL) and 30% H_2O_2 (45 mL), and stirred for 18 h at 25 °C. The mixture was diluted with Et_2O (300 mL) and water (100 mL), and the organic layer was separated. After extraction with Et_2O (3 × 200 mL), the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography (0–10% Et_2O in hexanes) to afford alcohol **24** (15.6 g, 63.7 mmol, 80%). **24**: colorless oil; $R_f = 0.60$ (25% Et_2O in hexanes); $[\alpha]_D^{25}$: −6.9 ($c = 1.1$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3483, 2960, 1260, 1094, 835, 780\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.86–5.79$ (m, 1H), 5.07 (dd, 2H, J = 13.0, 1.5 Hz), 3.90–3.86 (m, 1H), 3.82–3.77 (m, 1H), 3.70–3.66 (m, 1H), 3.13 (br s, 1H), 2.25–2.20 (m, 1H), 1.64–1.60 (m, 2H), 1.03 (d, 3H, J = 7.0 Hz), 0.88 (s, 9H), 0.059 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 140.8$, 115.1, 75.0, 62.8, 43.9, 35.4, 25.9, 25.8, 18.1, 15.6, −5.6, −5.7; HR-MS: calcd for $C_{13}H_{28}O_2Si$ $[M+Cs]^+$ 377.0911, found 377.0918.

Diol 25: A solution of 1M TBAF · THF (70 mL, 70 mmol) was added to a solution of alcohol **24** (14.3 g, 58.5 mmol) in THF (50 mL) at 25 °C. After stirring for 30 min, the reaction mixture was quenched with aqueous saturated ammonium chloride (50 mL) and diluted with Et_2O (150 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography (50–75% Et_2O in hexanes) to afford diol **25** (7.45 g, 57.3 mmol, 98%). **25**: colorless oil; $R_f = 0.45$ (70% Et_2O in hexanes). $[\alpha]_D^{25}$: −2.6 (c = 1.2, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3354, 2966, 2879, 1426, 1051, 909\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.76–5.69$ (m, 1H), 5.12 (d, 1H, J = 18.5 Hz), 5.12 (d, 1H, J = 10.5 Hz), 3.85–3.77 (m, 2H), 3.65–3.61 (m, 1H), 2.76 (br s, 2H), 2.33–2.19 (m, 1H), 1.72–1.69 (m, 1H), 1.64–1.61 (m, 1H), 1.01 (d, 3H, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 140.2$, 116.5, 74.9, 61.6, 44.5, 35.1, 15.8; HR-MS: calcd for $C_7H_{14}O_2$ $[M+Cs]^+$ 263.0045, found 263.0069.

Acetal 26: A solution of diol **25** (7.31 g, 56.3 mmol) in CH_2Cl_2 (60 mL) at 25 °C was treated with 4-methoxybenzaldehyde dimethylacetal (12.3 g, 67.6 mmol) and CSA (1.31 g, 5.63 mmol). After stirring for 6 h, the reaction was quenched with Et_3N (5 mL) and the mixture concentrated and purified by chromatography (0–10% Et_2O in hexanes) to afford the *p*-methoxybenzylidene acetal **26** (13.7 g, 55.2 mmol, 98%). **26**: colorless oil; $R_f = 0.55$ (25% Et_2O in hexanes); $[\alpha]_D^{25}$: −25.1 ($c = 1.2$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 3353, 2960, 1260, 1094, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.43$ (d, 2H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.4 Hz), 5.92 (m, 1H), 5.46 (s, 1H), 5.1–5.05 (m, 2H), 4.28–4.24 (m, 1H), 3.96–3.90 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 2.44–2.30 (m, 1H), 1.89–1.81 (m, 1H), 1.46–1.41 (m, 1H), 1.10 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.5$, 140.0, 131.3, 127.1, 114.7, 113.4, 100.9, 80.3, 67.0, 55.3, 42.5, 28.0, 15.2; HR-MS: calcd for $C_{15}H_{20}O_3$ $[M+Cs]^+$ 381.0464, found 381.0489.

Alcohol 27: A solution of acetal **26** (12.7 g, 51.2 mmol) in CH_2Cl_2 (100 mL) was treated at −78 °C with DIBAL-H (77 mL of a 1M solution in CH_2Cl_2, 77 mmol). After stirring for 30 min, the mixture was allowed to warm to 25 °C and stirred for 1.5 h. The reaction was quenched with methanol (10 mL), diluted with ethyl acetate (100 mL) and Rochelle salt (100 mL) and stirred vigorously for 2 h. After extraction with ethyl acetate (3 × 100 mL), the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography (10–25% Et_2O in hexanes) to afford alcohol **27** (11.6 g, 46.4 mmol, 91%). **27**: colorless oil; $R_f = 0.35$ (65% Et_2O in hexanes); $[\alpha]_D^{25}$: 93.8 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3409, 2966, 2873, 1617, 1513, 1254, 1051, 817\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$ (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J = 8.0 Hz), 5.81–5.73 (m, 1H), 5.08–5.04 (m, 2H), 4.59 (d, 1H, J = 11.5 Hz), 4.42 (d, 1H, J = 11.0 Hz), 3.79 (s, 3H), 3.71 (t, 2H, J = 5.5 Hz), 3.57–3.55 (m, 1H), 2.63–2.61 (m, 1H), 2.26 (br s, 1H), 1.71–1.64 (m, 2H), 1.04 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 159.3$, 140.6, 130.4, 129.5, 114.9, 113.9, 81.4, 71.2, 61.0, 55.2, 39.5, 32.1, 13.4; HR-MS: calcd for $C_{15}H_{22}O_3$ $[M+Cs]^+$ 383.0612, found 383.0638.

Olefin 28: A solution of alcohol **27** (11.6 g, 46.4 mmol) in CH_2Cl_2 (100 mL) was treated at 0 °C with imidazole (7.57 g, 111.3 mmol) and *tert*-butyldimethylsilylchloride (8.38 g, 55.6 mmol). After 1 h the reaction was diluted with aqueous saturated sodium bicarbonate (50 mL) and the reaction mixture was extracted with Et_2O (3 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (0–5% Et_2O in hexanes) to afford silyl ether **28** (16.4 g, 45.0 mmol, 97%). **28**: colorless oil; $R_f = 0.50$ (10% Et_2O in hexanes); $[\alpha]_D^{25}$: +27.8 ($c = 3.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2957, 2925, 2857, 1614, 1520, 1249, 1097, 836\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$ (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J =

8.0 Hz), 5.82–5.79 (m, 1H), 5.06 (d, 1H, J = 17.0 Hz), 5.06 (d, 1H, J = 14.0 Hz), 4.52 (d, 1H, J = 11.0 Hz), 4.44 (d, 1H, J = 11.0 Hz), 3.80 (s, 3H), 3.69 (t, 2H, J = 7.0 Hz), 3.52–3.49 (m, 1H), 2.53–2.50 (m, 1H), 1.67–1.61 (m, 2H), 1.04 (d, 3H, J = 6.5 Hz), 0.89 (s, 9H), 0.043 (s, 3H), 0.039 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 141.0, 131.2, 129.4, 114.6, 113.7, 79.0, 71.5, 59.9, 55.2, 40.3, 34.0, 25.9, 18.2, 14.5, −5.4, −5.5; HR-MS: calcd for $C_{21}H_{36}O_3Si$ $[M+Cs]^+$ 497.1486, found 497.1501.

Alcohol 29: A solution of alkene **28** (10.27 g, 28.2 mmol) in THF (100 mL) was cooled to −40 °C and treated with $BH_3 \cdot$THF (28 mL of 1M solution, 28 mmol). After stirring for 10 h, the reaction was cautiously quenched with 3N NaOH (93 mL) and 30% H_2O_2 (15 mL) and allowed to warm to 25 °C. Following extraction with Et_2O (3 × 100 mL) the organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (15–30% Et_2O in hexanes) to afford alcohol **29** (9.16 g, 24.0 mmol, 85%). **29**: colorless oil; R_f = 0.45 (66% Et_2O in hexanes); $[\alpha]_D^{25}$: +29.0 (c = 1.2, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 3403, 2966, 2929, 2861, 1611, 1519, 1248, 1094, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, 2H, J = 8.0 Hz), 6.87 (d, 2H, J = 8.0 Hz), 4.49 (d, 1H, J = 11.5 Hz), 4.45 (d, 1H, J = 11.5 Hz), 3.79 (s, 3H), 3.71–3.67 (m, 3H), 3.61–3.57 (m, 1H), 3.47–3.45 (m, 1H), 2.12–2.10 (m, 1H), 1.97–1.95 (m, 1H), 1.71–1.48 (m, 4H), 0.94 (d, 3H, J = 7.0 Hz), 0.88 (s, 9H), 0.035 (s, 3H), 0.032 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 130.8, 129.4, 113.8, 79.3, 71.5, 60.5, 59.8, 55.2, 35.5, 33.5, 32.4, 25.8, 18.1, 15.0, −5.4, −5.5; HR-MS: calcd for $C_{21}H_{38}O_4Si$ $[M+Cs]^+$ 515.1592, found 515.1610.

Iodide 11: A solution of alcohol **29** (4.78 g, 12.5 mmol), imidazole (2.04 g, 30.0 mmol) and triphenylphosphine (3.93 g, 15.0 mmol) in THF (50 mL) was treated at 0 °C with iodine (3.81 g, 15.0 mmol). After stirring for 30 min, the reaction was quenched with aqueous saturated sodium thiosulfate (50 mL) and aqueous saturated sodium bicarbonate (50 mL) and diluted with Et_2O (100 mL). The organic layer was separated, and the aqueous layer extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (0–5% Et_2O in hexanes) to afford iodide **11** (5.91 g, 12 mmol, 96%). **11**: light yellow oil; R_f = 0.55 (10% Et_2O in hexanes); $[\alpha]_D^{25}$: +16.1 (c = 1.0, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 2957, 2936, 2863, 1614, 1515, 1254, 1092, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (d, 2H, J = 8.0 Hz), 6.88 (d, 2H, J = 8.0 Hz), 4.50 (d, 1H, J = 11.5 Hz), 4.42 (d, 1H, J = 11.5 Hz), 3.80 (s, 3H), 3.69–3.66 (m, 2H), 3.47–3.45 (m, 1H), 3.28–3.27 (m, 1H), 3.18–3.15 (m, 1H), 1.98–1.86 (m, 2H), 1.71–1.55 (m, 3H), 0.91 (d, 3H, J = 7.0 Hz), 0.88 (s, 9H), 0.035 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 131.1, 129.4, 113.8, 78.2, 71.3, 59.8, 55.2, 36.5, 36.0, 33.3, 25.9, 18.2, 13.9, 5.5, −5.4, −5.5; HR-MS: calcd for $C_{21}H_{37}IO_3Si$ $[M+Cs]^+$ 625.0609, found 625.0631.

Ketone 30: A solution of iodide **11** (3.1 g, 6.3 mmol) in Et_2O (20 mL) at −78 °C was treated with *tert*-butyllithium (7.8 mL of a 1.7M solution in pentane, 13.2 mmol), added over a period of 10 min. After stirring at −78 °C for 30 min, the mixture was treated with a solution of aldehyde **9** (3.4 g, 8.8 mmol) in Et_2O (10 mL) added over a period of 10 min. After stirring at −78 °C for 30 min, the reaction mixture was quenched with water (100 mL) and extracted with Et_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (10–30% Et_2O in hexanes) to afford a diastereomeric mixture of alcohols at the C15 center (4.08 g, 5.4 mmol, 86%). A solution of the above mixture (4.08 g, 5.4 mmol) in CH_2Cl_2 (20 mL) was treated with Dess–Martin periodinane (2.8 g, 6.5 mmol) at 25 °C for 1 h. The mixture was then quenched with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1, 2 × 40 mL) and extracted with Et_2O (3 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by chromatography (0–15% Et_2O in hexanes) to afford ketone **23** (3.82 g, 5.1 mmol, 94%). **23**: colorless liquid; R_f = 0.6 (30% Et_2O in hexanes); $[\alpha]_D^{25}$: −12.9 (c = 1.3, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 2956, 1714, 1618, 1512, 1460, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, 2H, J = 8.0 Hz), 6.84 (d, 2H, J = 8.0 Hz), 4.48 (d, 1H, J = 11.2 Hz), 4.38 (d, 1H, J = 11.2 Hz), 4.05 (dd, 1H, J = 6.4, 8.0 Hz), 3.91 (t, 1H, J = 7.6 Hz), 3.80 (s, 3H), 3.75 (t, 1H, J = 8 Hz), 3.69 (t, 1H, J = 6.4 Hz), 3.45–3.43 (m, 1H), 2.60–2.40 (m, 4H), 1.71–1.56 (m, 12H), 1.42–1.27 (m, 6H), 0.91–0.81 (m, 12H), 0.89 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.041 (s, 3H), 0.037 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.5, 158.8, 130.9, 129.1, 113.6, 112.8, 80.7, 78.9, 71.2, 65.7, 59.9, 55.3, 41.0, 37.2, 36.0, 34.9, 33.2, 30.4, 29.3, 28.2, 27.0, 26.2, 26.1, 26.0, 25.8, 23.5, 18.8, 18.4, 14.5, 14.2, 8.6, 8.5, −1.8, −1.9, −5.0, −5.1; HR-MS: calcd for $C_{42}H_{78}O_7Si_2$ $[M+Cs]^+$ 883.4337, found 883.4360.

Spiroketal 31: A solution of ketone **30** (2.9 g, 3.85 mmol) in THF (5 mL) and tetra-*n*-butylammonium fluoride (11.6 mL of a 1.0M solution in THF, 11.6 mmol) was stirred at 50 °C for 2 h. The reaction mixture was diluted with Et_2O (100 mL) and washed with aqueous saturated ammonium chloride (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried and concentrated under reduced pressure. The crude lactol was redissolved in ethanol (20 mL) and subjected to hydrogenation under 10% Pd/C catalysis (0.29 g) at 25 °C for 12 h. The reaction mixture was filtered through a short pad of celite, concentrated, and subjected to flash chromatography to produce spiroketal **31** (1.18 g, 3.1 mmol, 80%). **31**: colorless liquid; R_f = 0.2 (15% Et_2O in hexanes); $[\alpha]_D^{25}$: +36.0 (c = 1.0, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 3458, 2947, 2879, 1463, 1383, 1082, 996 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.21 (t, 1H, J = 7.5 Hz), 4.0 (t, 1H, J = 7.5 Hz), 3.82–3.65 (m, 4H), 2.88 (br s, 1H), 2.12 (m, 1H), 1.95–1.79 (m, 4H), 1.71–1.44 (m, 10H), 1.41–1.24 (m, 6H), 0.91–0.80 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.3, 106.1, 87.3, 80.6, 75.8, 66.2, 60.4, 38.3, 35.6, 35.1, 34.9, 34.6, 30.1, 29.3, 29.0, 28.9, 25.8, 23.2, 17.5, 14.0, 8.1, 7.9; HR-MS: calcd for $C_{22}H_{40}O_5$ $[M+Cs]^+$ 517.1927, found 517.1941.

Aldehyde 32: A solution of alcohol **31** (1.18 g, 3.1 mmol) in CH_2Cl_2 (5 mL) was treated with Dess–Martin periodinane (1.9 g, 4.6 mmol) at 0 °C for 2 h. The mixture was then quenched with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1 2 × 20 mL) and extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (0–25% Et_2O in hexanes) to afford aldehyde **32** (1.1 g, 2.9 mmol, 94%). **32**: colorless liquid; R_f = 0.45 (30% Et_2O in hexanes); $[\alpha]_D^{25}$: +19.8 (c = 1.2, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 2962, 2925, 2878, 1731, 1465, 1087 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.82 (d, 1H, J = 1.5 Hz), 4.14 (t, 1H, J = 7.0 Hz), 3.97 (t, 1H, J = 7.0 Hz), 3.95–3.90 (m, 1H), 3.78 (t, 1H, J = 7.0 Hz), 2.58–2.54 (m, 1H), 2.40–2.36 (m, 1H), 2.08–2.03 (m, 1H), 1.95–1.91 (m, 1H), 1.82–1.55 (m, 11H), 1.42–1.28 (m, 6H), 0.94–0.83 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0, 122.4, 113.0, 106.4, 80.8, 72.2, 66.1, 47.4, 38.2, 35.3, 34.8, 34.7, 30.6, 29.2, 28.9, 28.8, 25.8, 23.3, 17.4, 14.0, 8.3, 7.9; HR-MS: calcd for $C_{22}H_{38}O_5$ $[M+Cs]^+$ 515.1772, found 515.1793.

Alkene 33: A solution of carbon tetrabromide (3.90 g, 11.7 mmol) in tetrahydrofuran (25 mL) was cooled to −25 °C and treated with HMPT (0.96 g, 5.85 mmol). After stirring for 15 min, a solution of aldehyde **32** (0.90 g, 2.35 mmol) in tetrahydrofuran (10 mL) was added dropwise and the mixture was stirred for 15 min. The reaction was quenched with aqueous saturated sodium bicarbonate (20 mL), the mixture was diluted with water (50 mL), and the organic layer was extracted with Et_2O (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was then subjected to flash chromatography to afford dibromide **33** (1.20 g, 2.23 mmol, 95%). **33**: colorless liquid; R_f = 0.65 (15% Et_2O in hexanes); $[\alpha]_D^{25}$: +18.3 (c = 1.25, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 2958, 2923, 2861, 1094, 835, 780 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.56 (t, 1H, J = 7.0 Hz), 4.13 (t, 1H, J = 7.0 Hz), 3.95 (t, 1H, J = 8.0 Hz), 3.88 (t, 1H, J = 7.0 Hz), 3.49–3.46 (m, 1H), 2.38–2.33 (m, 1H), 2.23–2.17 (m, 1H), 2.02–1.92 (m, 2H), 1.83–1.72 (m, 2H), 1.79–1.53 (m, 7H), 1.35–1.20 (m, 8H), 0.94–0.83 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.0, 125.6, 113.0, 106.5, 74.3, 65.9, 38.3, 36.8, 34.7, 34.6, 34.1, 30.3, 29.6, 29.1, 29.0, 28.6, 25.9, 23.3, 17.5, 14.0, 8.4, 7.9; HR-MS: calcd for $C_{22}H_{31}NO_4Si$ $[M+Cs]^+$ 534.1073, found 534.1099.

Alkyne 8: A solution of the dibromoalkene **33** (104 mg, 0.19 mmol) in THF (3 mL) was cooled at −78 °C and treated with *n*-butyllithium (254 μL of a 1.6M solution in hexanes, 0.40 mmol). Stirring was continued for 20 min at −78 °C and for 20 min at −20 °C. The reaction mixture was then cooled at −78 °C, treated with freshly distilled iodomethane (60 μL, 0.96 mmol) and subsequently allowed to warm to 0 °C where it was stirred for a period of 1 h. The solution was then quenched with water (1 mL), diluted with Et_2O (30 mL) and washed with brine (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (0–15% Et_2O in hexanes) to give alkyne **8** (72 mg, 18.4 μmol, 95%). **8**: colorless liquid; R_f = 0.65 (15% Et_2O in hexanes); $[\alpha]_D^{25}$: +2.14 (c = 0.84, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 2957, 2931, 2878, 1463, 1087, 930 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.25 (t, 1H, J = 7.5 Hz), 3.98–3.95 (m, 2H), 3.47–3.42 (m, 1H), 2.41–2.37 (m, 1H), 2.30–2.28 (m, 1H), 2.05–2.00 (m, 2H), 1.79–1.42 (m, 14H), 1.34–1.25 (m, 6H), 0.94–0.82 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 112.8, 106.7, 87.1, 81.0, 76.1, 74.4, 66.0, 38.3, 34.53, 34.5, 33.8, 31.6, 29.1, 29.0, 28.6, 25.9, 23.6, 23.3, 17.5, 14.0, 8.4, 7.9, 3.5; HR-MS: calcd for $C_{24}H_{40}O_4$ $[M]^+$ 393.3005, found 393.3017.

Triacetate 34: A solution of alcohol **31** (102 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) was treated with pyridine (63 μL, 0.8 mmol) and acetic anhydride

0947-6539/00/0611-1996 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

(40 μL, 0.40 mmol) at 25 °C for 15 min. The reaction mixture was diluted with Et_2O (20 mL) and washed with ammonium chloride (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated, and the residue purified by chromatography (0–25 % Et_2O in hexanes). The acetylated product was dissolved in CH_2Cl_2/MeOH 9:1 (6 mL) and treated with CSA (26 μmol) at 25 °C for 3 h. The reaction was quenched with excess triethylamine and the residue was filtered through a short pad of silica gel and concentrated. The crude diol was redissolved in CH_2Cl_2 (2 mL) and treated with triethylamine (160 mg, 1.6 mmol) and acetic anhydride (80 μL, 0.80 mmol) at 25 °C for 3 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with ammonium chloride (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated, and the residue purified by chromatography (0–25 % Et_2O in hexanes) to afford triacetate **34** (86.8 mg, 0.19 mmol, 74 % over three steps). **34**: colorless liquid; $R_f = 0.45$ (30 % Et_2O in hexanes); $[\alpha]_D^{25}$: +37.5 ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2931, 2868, 1745, 1463, 1369, 1238, 1050, 1083, 993, 923\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.19$ (dd, 1H, $J = 9.0$, 2.5 Hz), 4.52 (dd, 1H, $J = 12.0$, 2.0 Hz), 4.34–4.26 (m, 1H), 4.24 (dd, 1H, $J = 12.0$, 8.5 Hz), 4.18–4.13 (m, 1H), 3.49 (ddd, 1H, $J = 10.8$, 8.0, 2.8 Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96–1.50 (m, 11H), 1.31–1.25 (m, 6H), 0.91 (t, 3H, $J = 7.0$ Hz), 0.87 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 171.27, 171.25, 170.4, 107.0, 86.2, 73.6, 63.9, 61.7, 38.4, 34.5, 34.4, 34.2, 32.1, 31.3, 29.6, 29.0, 25.4, 23.1, 21.0, 20.9, 20.7, 17.6, 14.0; HR-MS: calcd for $C_{23}H_{38}O_8$ $[M+Cs]^+$ 575.1619, found 575.1632.

Oxazolidinone 43: A solution of imide **42** (1.15 g, 4.94 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C, treated with triethylamine (0.56 mL, 5.41 mmol) and dibutylborontriflate (4.95 mL, 4.95 mmol, 1M in CH_2Cl_2). The solution was stirred for 30 min at −78 °C and then allowed to warm to 0 °C over a period of 1 h. The mixture was recooled to −78 °C, treated with aldehyde **41** (1.00 g, 5.94 mmol) in CH_2Cl_2 (5 mL), stirred at −78 °C for 30 min, and warmed to 0 °C over a 2 h period. The resulting mixture was treated with a solution of sodium acetate (4.2 g) in MeOH (70 mL) into which 30 % H_2O_2 (5.6 mL) was added and stirred for 30 min from 0 to 25 °C. The reaction mixture was diluted with water (150 mL), hexane (100 mL), and separated. The organic layer was washed with brine (25 mL), dried ($MgSO_4$), concentrated, and subjected to flash chromatography (10–30 % Et_2O in hexanes) to afford **43** (1.58 g, 3.95 mmol, 80 %). **43**: colorless liquid; $R_f = 0.45$ (50 % Et_2O in hexanes); $[\alpha]_D^{25}$: 7.5 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3471, 2960, 2929, 2855, 1777, 1697, 1470, 1371, 1199\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.42–7.34$ (m, 3H), 7.29–7.27 (m, 2H), 5.66 (d, 1H, $J = 9.0$ Hz), 4.78 (t, 1H, $J = 8.5$ Hz), 4.72 (d, 1H, $J = 6.0$ Hz), 4.00–3.94 (m, 1H), 3.01–2.83 (m, 1H), 1.39 (d, 3H, $J = 9.0$ Hz), 0.92 (s, 9H), 0.88 (d, 3H, $J = 8.0$ Hz), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.7$, 152.3, 132.8, 128.7, 128.6, 125.4, 104.3, 88.6, 79.0, 63.7, 54.8, 44.1, 26.1, 16.6, 14.5, 12.2, −4.57, −4.59; HR-MS: calcd for $C_{22}H_{31}NO_4Si$ $[M+Cs]^+$ 534.1074, found 534.1099.

Amide 44: A suspension of *N,O*-dimethyl-hydroxylamine hydrochloride (3.65 g, 37.4 mmol) in THF (6 mL) was cooled to −30 °C and treated with $AlMe_3$ (18.7 mL, 37.4 mmol, 2.0M in toluene) over a 5 min period. After the addition was complete, the solution was warmed to 25 °C and stirred for 15 min. The clear solution was cooled to −10 °C, and treated with imide **43** (1.67 g, 4.16 mmol) in THF (15 mL) added dropwise. The resulting mixture was warmed to 0 °C and stirred for 2 h. The reaction mixture was poured onto a mixture containing Rochelle salt (100 mL), aqueous saturated sodium bicarbonate (50 mL) and ethyl acetate (150 mL) at 0 °C and alllowed to warm to 25 °C under vigorous stirring. After 20 min, the resulting mixture was partitioned, the organic layer separated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The organic layers were collected, dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash chromatography (15–30 % Et_2O in hexanes) to yield the corresponding Weinreb amide (1.07 g, 3.75 mmol, 90 %) as a sticky oil. $R_f = 0.35$ (66 % Et_2O in hexanes). A solution of the Weinreb amide (995 mg, 3.67 mmol) in THF (3 mL) was treated with TBAF · SiO_2 (7.3 g, 7.34 mmol) at 25 °C for 3 h. The reaction mixture was filtered through a short pad of silica, concentrated and taken on crude to the next step. A solution of the crude alcohol and 2,6-lutidine (1.30 mL, 10.9 mmol) in CH_2Cl_2 (5 mL) was treated at 25 °C with triisopropylsilyl trifluoromethanesulfonate (1.50 mL, 5.58 mmol). After 15 min, the mixture was quenched with aqueous saturated sodium bicarbonate (10 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated, and the organic layer was washed with brine (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (10–20 % Et_2O in hexanes) to give amide **44** (938 mg, 3.38 mmol, 81 % yield over three steps). **44**: colorless liquid; $R_f = 0.3$ (30 % Et_2O in hexanes); $[\alpha]_D^{25}$: +48.0 ($c = 1.2$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2939, 2869, 1651, 1460, 1418, 1390, 1115, 1064, 994, 882\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.63$ (dd, 1H, $J = 7.5$, 1.5 Hz), 3.70 (s, 3H), 3.16 (s, 3H), 3.16 (m, 1H), 2.36 (d, 1H, $J = 2.0$ Hz), 1.22 (d, 3H, $J = 6.5$ Hz), 1.14–1.02 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.7$, 97.2, 84.6, 73.0, 64.5, 61.4, 44.0, 17.9, 13.9, 12.2; HR-MS: calcd for $C_{17}H_{33}O_3NSi$ $[M+Cs]^+$ 460.1282, found 460.1298.

Ester 40: A solution of amide **44** (1.55 g, 4.74 mmol) in THF (30 mL) was cooled at −78 °C and treated with DIBAL-H (7.9 mL of a 1.5M solution in toluene, 11.8 mmol). After stirring for 30 min at −78 °C, the reaction mixture was quenched with methanol (3 mL), diluted with ethyl acetate (50 mL), allowed to warm to 25 °C and stirred for 30 min with a saturated solution of Rochelle salt (100 mL). The mixture was extracted with ethyl acetate (3 × 50 mL) and the organic layer was dried ($MgSO_4$) and concentrated to produce the crude aldehyde, that was used for the next step without any purification. A solution of the above aldehyde in CH_2Cl_2 (10 mL) was treated with $Ph_3P{=}CH\text{-}CO_2TMSE$ (**45**) (5.07 g, 11.85 mmol) for 15 h, at 25 °C. The reaction mixture was then concentrated and subjected to flash chromatography (0–5 % Et_2O in hexanes) to afford ester **40** (1.76 g, 4.31 mmol, 91 %). **40**: colorless liquid; $R_f = 0.65$ (15 % Et_2O in hexanes); $[\alpha]_D^{25}$: +10.6 ($c = 0.5$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2946, 2863, 1719, 1466, 1253, 1175, 860, 836\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.07$ (dd, 1H, $J = 16$, 7.5 Hz), 5.86 (d, 1H, $J = 16.5$ Hz), 4.46 (dd, 1H, $J = 5.0$, 2.0 Hz); 4.22 (t, 2H, $J = 8.0$ Hz), 2.60 (q, 1H, $J = 6.0$ Hz), 2.40 (d, 1H, $J = 2.0$ Hz), 1.14 (d, 3H, $J = 6.5$ Hz), 1.07–0.99 (m, 23H), 0.026 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.8$, 149.5, 122.3, 83.1, 73.9, 66.4, 62.3, 43.6, 17.92, 17.90, 17.1, 14.6, 12.1, −1.6; HR-MS: calcd for $C_{22}H_{42}O_3Si_2$ $[M+Cs]^+$ 543.1725, found 543.1739.

Vinyl stannane 37: A solution of ester **40** (726 mg, 1.86 mmol) in benzene (10 mL) was treated at 5 °C with dichlorobistriphenylphosphinepalladium(II) (26 mg, 0.037 mmol) and tri-*n*-butyltin hydride (750 μL, 2.8 mmol). After stirring at 5 °C for 10 min, the reaction mixture was concentrated and subjected to flash chromatography (0–10 % Et_2O in hexanes) to afford stannane **37** (1.14 g, 1.70 mmol, 91 %). **37**: colorless liquid; $R_f = 0.85$ (10 % Et_2O in hexanes); $[\alpha]_D^{25}$: +8.4 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2957, 2925, 2868, 1719, 1463, 1254, 1175, 867, 836\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.07$ (dd, 1H, $J = 16$, 7.5 Hz), 6.04–6.0 (d, 1H, $J = 19.5$ Hz), 5.85 (dd, 1H, $J = 19.0$, 7.0 Hz), 5.76 (d, 1H, $J = 15.5$ Hz), 4.20 (t, 2H, $J = 8.5$ Hz), 4.12–4.10 (m, 1H), 2.53 (q, 1H, $J = 6.5$ Hz), 1.48–1.42 (m, 4H), 1.30–1.24 (m, 6H), 1.04–1.02 (m, 26H), 0.87 (t, 9H, $J = 7.5$ Hz), 0.88–0.85 (m, 8H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.9$, 151.1, 148.8, 130.0, 121.2, 80.6, 62.2, 43.3, 29.0, 21.2, 18.1, 18.0, 13.6, 12.3, 9.4, −1.6; HR-MS: calcd for $C_{34}H_{70}O_3Si_2Sn$ $[M+Cs]^+$ 835.2946, found 835.2959.

Vinyl iodide 39: A solution of vinyl stannane **37** (202 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C and titrated with a saturated solution of iodine in CH_2Cl_2, until the iodine color persisted. The solution was then stirred for 5 min and partitioned between a solution of CH_2Cl_2 (20 mL) and aqueous saturated sodium thiosulfate (20 mL). The organic layer was collected, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (0–10 % Et_2O in hexanes) to afford compound **39** (140 mg, 0.26 mmol, 90 %). **39**: colorless liquid; $R_f = 0.65$ (10 % Et_2O in hexanes); $[\alpha]_D^{25}$: +39.6 ($c = 1.0$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2951, 2863, 1719, 1651, 1463, 1254, 1175, 862, 841\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.01$ (dd, 1H, $J = 16.0$, 7.0 Hz), 6.46 (dd, 1H, $J = 14.5$, 7.0 Hz), 6.26 (d, 1H, $J = 15.0$ Hz), 5.80 (d, 1H, $J = 15.5$ Hz), 4.23 (t, 2H, $J = 8.0$ Hz), 4.17 (dd, 1H, $J = 5.0$, 7.5 Hz), 2.53 (m, 1H), 1.04–1.03 (m, 26H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.7$, 149.4, 146.3, 122.1, 78.9, 77.8, 62.4, 42.8, 18.0, 17.9, 17.2, 14.3, 12.2, −1.6. HR-MS: calcd for $C_{22}H_{43}O_3Si_2I$ $[M+Cs]^+$ 671.0849, found 671.0859.

Vinyl iodide 36: A solution of alkyne **8** (200 mg, 0.51 mmol) in THF (2 mL) was introduced dropwise into a stirred solution of bis(cyclopentadienyl)-zirconium chloride hydride (263 mg, 1.02 mmol) in THF (2 mL). The mixture was protected from the light and allowed to stir at 25 °C for 8 h. The solution was then cooled at 0 °C and treated with a saturated solution of iodine in CCl_4, added dropwise until the iodine color persisted. The reaction mixture was then diluted with Et_2O (20 mL) and washed with saturated aqueous sodium thiosulfate (2 × 20 mL). The organic layer was dried ($MgSO_4$), filtered through a short pad of celite and concentrated

under reduced pressure. Flash chromatography (0–10% Et_2O in hexanes) gave iodide **5** (142 mg, 27.3 μmol, 53%) together with the C9 *trans*-iodide (57 mg, 11 μmol, 21%), that was taken to the next step without any further purification. **36**: colorless liquid; $R_f = 0.6$ (10% Et_2O in hexanes); IR (film): $\tilde{\nu}_{max} = 2925$, 2863, 1463, 1379, 1186, 1087, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.25$ (t, 1H, $J = 7.0$ Hz), 4.05 (t, 1H, $J = 6.5$ Hz), 3.90 (t, 1H, $J = 6.5$ Hz), 3.62 (t, 1H, $J = 6.5$ Hz), 3.46–3.40 (m, 1H), 2.35 (s, 3H), 2.30–2.20 (m, 2H), 2.05–1.86 (m, 6H), 1.6–1.4 (m, 9H), 1.31–1.24 (m, 4H), 0.92–0.81 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 138.2$, 112.2, 106.5, 94.5, 85.6, 80.1, 74.7, 65.5, 45.8, 40.2, 38.6, 34.4, 34.1, 33.8, 32.3, 29.7, 29.0, 27.7, 26.9, 23.5, 17.6, 14.1, 8.3, 8.0; HR-MS: calcd for $C_{24}H_{41}O_4I$ $[M - C_2H_5]^+$ 491.1658, found 491.1675.

Ester 35: (by Stille coupling of **36** with **37**): A solution of iodide **36** (150 mg, 0.29 mmol) and stannane **37** (136 mg, 0.20 mmol) in DMF/THF 1:1 (1 mL) was added dropwise to a stirred solution of bis(acetonitrile)dichloropalladium(II) (2.5 mg, 9.6 μmol) in DMF/THF 1:1 (1 mL) at 25 °C. After stirring for 15 h the reaction mixture was diluted with aqueous saturated sodium bicarbonate (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (0–10% Et_2O in hexanes) to afford compound **35** (84 mg, 0.11 mmol, 52%).

Ester 35: (by modified Negishi coupling of **8** with **39**): A solution of alkyne **8** (99 mg, 0.25 mmol) and bis(cyclopentadienyl)zirconium-chloride-hydride (131 mg, 0.51 mmol) in tetrahydrofuran (1 mL) was stirred at 50 °C under argon for 2 h in the dark. The resulted yellow solution was allowed to cool to 25 °C and treated with a freshly prepared solution of anhydrous zinc chloride (104 mg, 0.76 mmol) in tetrahydrofuran (0.8 mL), added via cannula. The reaction mixture was stirred for 5 min and subsequently treated with a solution of vinyl iodide **39** (165 mg, 0.31 mmol) and palladium tetrakistriphenylphosphine (15 mg, 0.012 mmol) in tetrahydrofuran (2 mL). The reaction was stirred for 2 h, then diluted with water (10 mL), and extracted with Et_2O (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (0–5% Et_2O in hexanes) to afford compound **35** (168 mg, 0.21 mmol, 84% over two steps). **35**: colorless liquid; $R_f = 0.45$ (10% Et_2O in hexanes); $[\alpha]_D^{25}$: +12.1 ($c = 0.93$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2936$, 2863, 1719, 1651, 1463, 1254, 1170, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.10$ (dd, 1H, $J =$ 7.0, 16.0 Hz), 6.08 (d, 1H, $J = 16.0$ Hz), 5.76 (d, 1H, $J = 16.0$ Hz), 5.56 (t, 1H, $J = 7.5$ Hz), 5.42 (dd, 1H, $J = 8.5$, 15.5, Hz), 4.23–4.14 (m, 4H), 3.93–3.89 (m, 2H), 3.48–3.44 (m, 1H), 2.56–2.53 (m, 1H), 2.41–2.37 (m, 1H), 2.26–2.21 (m, 1H), 1.92–1.89 (m, 1H), 1.81–1.24 (m, 21H), 1.02-.98 (m, 21H), 0.93–0.87 (m, 14H), 0.81 (d, 3H, $J = 6.5$ Hz), 2.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.0$, 151.2, 136.4, 134.0, 129.3, 126.9, 121.3, 112.7, 106.5, 86.9, 81.0, 77.8, 77.2, 75.4, 65.9, 62.2, 43.9, 38.3, 34.7, 34.2, 32.1, 31.4, 29.2, 29.18, 28.8, 26.0, 23.3, 18.1, 18.0, 17.7, 17.1, 14.2, 14.1, 12.6, 12.3, 8.4, 7.9, −1.6; HR-MS: calcd for $C_{46}H_{84}O_7Si_2$ $[M+Cs]^+$ 937.4810, found 937.4835.

Allylic alcohol 47: $Ph_3P{=}CHCO_2CH_2CH_2TMS$ (**35**) (34.1 g, 81 mmol) was added to a solution of 1-hydroxyacetone (**46**) (5.0 g, 67.6 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred at 25 °C for 24 h. The solvent was then removed under reduced pressure and the residue subjected to flash chromatography (15–35% Et_2O in hexanes) to afford **47** (12.4 g, 57.4 mmol, 85%). **47**: colorless liquid; $R_f = 0.45$ (60% Et_2O in hexanes); IR (film): $\tilde{\nu}_{max} = 3446$, 2947, 2892, 1716, 1654, 1229, 1149, 1057, 848 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.96$ (s, 1H), 4.20 (t, 2H, $J = 8.0$ Hz), 4.13 (s, 2H), 2.08 (s, 3H), 1.80 (br s, 1H), 1.00 (t, 2H, $J = 8.0$ Hz), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.1$, 157.0, 114.0, 67.1, 61.9, 17.3, 15.5, −1.6; HR-MS: calcd for $C_{10}H_{20}O_3Si$ $[M+Cs]^+$ 349.0234, found 349.0251.

Aldehyde 48: A solution of alcohol **47** (4.1 g, 18.1 mmol) in CH_2Cl_2 (20 mL) was added via cannula to a stirred suspension of pyridinium chlorochromate absorbed on celite (8.2 g, 38.1 mmol) in CH_2Cl_2 (100 mL). After stirring for 2 h at 25 °C, the mixture was diluted with hexanes (50 mL), filtered through a pad of celite and washed with Et_2O (2 × 50 mL). The solvents were removed under reduced pressure and the residue subjected to flash chromatography (0–10% Et_2O in hexanes) to produce aldehyde **48** (3.41 g, 15.9 mmol, 88%). **48**: colorless liquid; $R_f = 0.4$ (25% Et_2O in hexanes); IR (film): $\tilde{\nu}_{max} = 2957$, 2899, 1719, 1222, 1165, 1045, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.58$ (s, 1H), 6.46 (s, 1H), 4.28 (t, 2H, $J =$ 8.5 Hz), 4.13 (s, 2H), 2.17 (s, 3H), 1.80 (br s, 1H), 1.04 (t, 2H, $J = 8.5$ Hz), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 194.7$, 165.8, 150.3, 135.8, 63.3, 17.2, 10.6, −1.7; HR-MS: calcd for $C_{10}H_{18}O_3Si$ $[M+Cs]^+$ 347.0077, found 347.0096.

Iodide 6: A solution of aldehyde **48** (2.0 g, 9.33 mmol) in tetrahydrofuran (60 mL) was cooled to 0 °C and treated with chromium(II) chloride (9.17 g, 74.6 mmol) and iodoform (9.2 g, 23.3 mmol). After stirring for 0.5 h, the mixture was diluted with hexanes (25 mL), filtered over celite, washed with Et_2O (2 × 10 mL), concentrated under reduced pressure, and purified by chromatography (0–5% Et_2O in hexanes) to yield vinyl iodide **6** (2.05 g, 6.06 mmol, 65%). **6**: light yellow oil; $R_f = 0.4$ (5% Et_2O in hexanes); IR (film): $\tilde{\nu}_{max} = 2957$, 1719, 1619, 1243, 1154, 1055, 951, 836 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) $\delta = 6.75$ (d, 1H, $J = 14.5$ Hz), 6.28 (d, 1H, $J = 14.8$ Hz), 5.57 (s, 1H), 4.21–4.17 (m, 2H), 2.01 (s, 3H), 0.89 (t, 2H, $J = 8.5$ Hz), −0.96 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) $\delta = 166.1$, 150.9, 148.2, 120.9, 85.0, 62.3, 17.9, 13.5, −1.0; HR-MS: calcd for $C_{11}H_{19}IO_2Si$ $[M+Cs]^+$ 470.9251, found 470.9270.

Diol 49: A solution of ester **35** (100 mg, 0.124 mmol) in MeOH (5 mL) was treated with pyridinium *p*-toluenesulfonate (94 mg, 0.374 mmol) at 40 °C. After 3 h, the reaction mixture was quenched with Et_3N (2 mL), concentrated, and subjected to flash chromatography (10–25% Et_2O in hexanes) to afford diol **49** (69 mg, 0.093 mmol, 75%). **49**: colorless liquid; $R_f = 0.3$ (30% Et_2O in hexanes); $[\alpha]_D^{25}$: +7.08 ($c = 0.8$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3434$, 2960, 2923, 2867, 1716, 1463, 1377, 1254, 1082, 860, 842 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) $\delta = 7.47$ (dd, 1H, $J = 7.0$, 15.5 Hz), 6.36 (d, 1H, $J = 16.0$ Hz), 6.08 (d, 1H, $J = 15.5$ Hz), 5.88 (t, 1H, $J = 7.5$ Hz), 5.65 (dd, 1H, $J = 7.5$, 15.5 Hz), 4.28–4.21 (m, 4H), 3.95–3.93 (m, 1H), 3.78–3.76 (m, 1H), 3.62–3.55 (m, 1H), 2.55–2.34 (m, 2H), 2.25–2.20 (m, 1H), 1.98–1.93 (m, 1H), 1.72 (s, 3H), 1.39–1.26 (m, 16H), 1.13–1.11 (m, 21H), 1.02 (d, 3H, $J = 7.0$ Hz), 0.91–0.88 (m, 2H), 0.85 (t, 3H, $J = 7.5$ Hz), 0.64 (d, 3H, $J =$ 7.0 Hz), 0.096 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) $\delta = 166.8$, 151.1, 136.8, 134.8, 129.3, 128.3, 127.6, 122.1, 106.5, 90.1, 78.0, 77.0, 76.4, 63.6, 62.2, 44.3, 39.4, 36.4, 35.0, 34.4, 32.2, 29.2, 28.9, 25.7, 23.4, 18.3, 18.2, 17.5, 17.3, 14.8, 14.1, 12.6, −1.8; HR-MS: calcd for $C_{41}H_{76}O_7Si_2$ $[M+Cs]^+$ 869.4184, found 869.4199.

Aldehyde 50: A solution of the diol **49** (58.0 mg, 0.079 mmol) in THF (2 mL) and H_2O (1 mL) was cooled to 0 °C and treated with sodium periodate (0.101 g, 0.474 mmol). After 10 min, the solution was warmed to 25 °C and stirred for 2 h. The reaction mixture was diluted with Et_2O (20 mL) and partitioned with aqueous saturated sodium bicarbonate (5 mL). The organic layers were collected, washed with water (2 × 5 mL), dried ($MgSO_4$), and concentrated. The crude residue was subjected to flash chromatography (0–5% Et_2O in hexanes) to afford aldehyde **50** (52.9 mg, 0.075 mmol, 95%). **50**: colorless liquid; $R_f = 0.4$ (5% Et_2O in hexanes); $[\alpha]_D^{25}$: +40.3 ($c = 0.65$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2962$, 2863, 1719, 1651, 1463, 1249, 1175, 1066, 862, 841 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) $\delta = 9.67$ (s, 1H), 7.48 (dd, 1H, $J = 7.5$, 16.5 Hz), 6.36 (d, 1H, $J = 15.5$ Hz), 6.09 (d, 1H, $J = 15.5$ Hz), 5.73 (t, 1H, $J = 6.5$ Hz), 5.66 (dd, 1H, $J = 7.5$, 15.5 Hz), 4.31 (dd, 1H, $J = 4.0$, 8.0 Hz), 4.27–4.23 (m, 2H), 3.61–3.57 (m, 1H), 2.57–2.55 (m, 1H), 2.37–2.32 (m, 1H), 2.14–2.11 (m, 1H), 1.92–1.80 (m, 1H), 1.67 (s, 3H), 1.95–1.61 (m, 13H), 1.16–1.12 (m, 21H), 1.04 (d, 3H, $J = 6.5$ Hz), 0.91 (t, 2H, $J = 8.0$ Hz), 0.80 (t, 3H, $J = 7$ Hz), 0.67 (d, 3H, $J =$ 6.5 Hz), −0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) $\delta = 203.4$, 166.4, 150.9, 136.9, 134.3, 129.8, 127.5, 122.2, 107.2, 90.4, 78.2, 76.9, 62.0, 44.3, 38.1, 35.0, 34.5, 33.8, 31.9, 29.4, 29.3, 25.5, 23.2, 18.3, 18.2, 17.5, 17.3, 14.6, 13.9, 12.6, 12.5, −1.7; HR-MS: calcd for $C_{40}H_{72}O_5Si_2$ $[M+Cs]^+$ 821.3973, found 821.3992.

Coupling of 6 with 50: A solution of aldehyde **50** (64 mg, 93 μmol) and vinyl iodide **6** (123 mg, 0.363 mmol) in dry DMF (3 mL) was treated under argon with chromium(II) chloride (274 mg, 2.2 mmol) and nickel(II) chloride (1.4 mg, 0.01 mmol). After stirring for 2 h at 25 °C, the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography (preparative silica gel plate, 15% Et_2O in hexanes) to yield a 1:1.2 mixture of diastereomeric alcohols **5** and **51** (combined amount: 55.2 mg, 60 μmol, 65%). The minor diastereomer **5** was shown to have the desired stereochemistry (*S*) at the C19 carbon center (NOE studies). Major diastereomer **51**: (*R*)-stereochemistry at C19, 30.1 mg, 32.7 μmol, 35%; colorless liquid; $R_f = 0.4$ (15% Et_2O in hexanes); $[\alpha]_D^{25}$: −24.5 ($c = 0.4$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3843$, 2953, 2867, 1722, 1463, 1260, 1162, 860, 842 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) $\delta = 7.48$ (dd, 1H, $J =$ 7.0, 16.0 Hz), 6.70 (d, 1H, $J = 16.0$ Hz), 6.35 (d, 1H, $J = 15.5$ Hz), 6.14 (dd, 1H, $J = 5.5$, 15.5 Hz), 6.10–6.04 (m, 2H), 5.89 (t, 2H, $J = 7.5$ Hz), 5.64 (dd, 1H, $J = 7.5$, 15.5 Hz), 4.46 (d, 1H, $J = 6.0$ Hz), 4.27–4.22 (m, 5H), 3.71–3.67 (m, 1H), 3.61 (br s, 1H), 2.57–2.44 (m, 1H), 2.47 (s, 3H), 2.42–2.36

0947-6539/00/0611-1998 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 11

(m, 1H), 2.35–2.21 (m, 1H), 2.06–1.98 (m, 1H), 1.70 (s, 3H), 1.58–1.20 (m, 15H), 1.13–1.08 (m, 21H), 1.01 (d, 3H, J = 7.0 Hz), 0.10–0.92 (m, 4H), 0.88 (t, 3H, J = 6.5 Hz), 0.65 (d, 3H, J = 6.5 Hz), −0.08 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ = 166.9, 166.5, 151.8, 150.9, 136.8, 135.1, 135.0, 134.8, 128.9, 127.7, 122.2, 120.2, 107.2, 91.6, 78.1, 77.3, 76.5, 62.1, 62.6, 44.2, 39.4, 37.5, 35.1, 34.1, 32.0, 29.2, 27.9, 27.7, 25.7, 23.4, 18.3, 18.2, 17.5, 17.4, 17.3, 14.6, 14.1, 13.9, 12.6, −1.74, −1.75; HR-MS: calcd for $C_{51}H_{92}O_8Si_3$ $[M+Cs]^+$ 1049.5154, found 1049.5189. Minor diastereomer **5**: (*S*)-stereochemistry at C19; 25.1 mg, 27.3 μmol, 30%; colorless liquid; R_f = 0.38 (15% Et_2O in hexanes); $[\alpha]_D^{25}$: −25.5 (c = 0.4, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 3843, 2953, 2867, 1722, 1463, 1260, 1162, 860, 842 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ = 7.45 (dd, 1H, J = 7.2, 15.6 Hz), 6.60 (d, 1H, J = 16.0 Hz), 6.34–6.25 (m, 2H), 6.08–6.03 (m, 2H), 5.86 (t, 1H, J = 7.0 Hz), 5.65 (dd, 1H, J = 8.0, 16.0 Hz), 4.29–4.25 (m, 4H), 4.19–4.17 (m, 1H), 3.72–3.69 (m, 1H), 3.62–3.57 (m, 1H), 2.53–2.50 (m, 1H), 2.47 (s, 3H), 2.42–2.21 (m, 1H), 2.04–1.99 (m, 1H), 1.72 (s, 3H), 1.60–1.20 (m, 15H), 1.13–1.08 (m, 21H), 1.02 (d, 3H, J = 7.2 Hz), 0.91–0.88 (m, 4H), 0.87 (t, 3H, J = 6.4 Hz), 0.66 (d, 3H, J = 6.4 Hz), −0.07 (s, 18H); ^{13}C NMR (125 MHz, C_6D_6) δ = 166.9, 166.4, 151.8, 150.9, 136.7, 135.3, 135.0, 134.9, 129.0, 127.6, 122.2, 120.2, 107.2, 90.8, 78.1, 77.9, 77.4, 62.0, 61.6, 44.2, 39.5, 34.8, 34.1, 32.1, 30.1, 30.0, 29.2, 26.1, 23.4, 18.3, 18.2, 17.5, 17.4, 17.3, 14.4, 14.1, 13.9, 12.7, −1.7; HR-MS: calcd for $C_{51}H_{92}O_8Si_3$ $[M+Cs]^+$ 1049.5154, found 1049.5172.

Ketone 52: A solution of alcohol **51** (14.1 mg, 15.3 μmol) in CH_2Cl_2 (0.3 mL) was treated at 25 °C with Dess–Martin periodinane (9.9 mg, 23.1 μmol). After stirring for 2 h, the mixture was quenched with aqueous saturated sodium bicarbonate/sodium thiosulfate (1:1 2 × 10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (0–15% Et_2O in hexanes) to afford ketone **52** (13.1 g, 14.3 μmol, 93%). **52**: $[\alpha]_D^{25}$: −42.1 (c = 1.07, CH_2Cl_2); 2957, 2863, 1719, 1599, 1468, 1254, 1228, 1160, 867, 841 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ = 7.55 (dd, 1H, 7.5, 16.5 Hz), 7.51 (dd, 1H, J = 15.5, 6.5 Hz), 7.26 (d, 1H, J = 15.5 Hz), 6.38 (d, 1H, J = 15.5 Hz), 6.18 (s, 1H), 6.13 (d, 1H, J = 15.5 Hz), 5.72 (t, 1H, J = 6.5 Hz), 5.67 (dd, 1H, J = 15.5, 8.0 Hz), 4.36 (dd, 1H, J = 8.0, 4.5 Hz), 4.26–4.22 (m, 4H), 3.56–3.50 (m, 1H), 2.86–2.80 (m, 1H), 2.64–2.60 (m, 1H), 2.42 (d, 3H, J = 1.0 Hz), 2.38–2.33 (m, 1H), 2.13–2.07 (m, 1H), 1.92–1.88 (m, 1H), 1.65 (s, 3H), 1.62–1.26 (m, 13H), 1.16–1.10 (m, 21H), 0.94–0.89 (m, 7H), 0.80 (t, 3H, 7.0 Hz), 0.68 (d, 3H, J = 6.5 Hz), −0.08 (s, 9H), −0.09 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 200.8, 166.4, 166.2, 150.9, 149.8, 145.2, 137.2, 133.9, 129.4, 128.3, 127.7, 127.0, 126.7, 122.3, 107.1, 91.6, 78.3, 76.7, 62.2, 62.0, 53.1, 44.4, 38.4, 38.0, 34.3, 31.9, 30.2, 30.0, 29.4, 25.9, 23.2, 18.3, 18.2, 17.7, 17.4, 14.6, 13.9, 13.6, 12.7, −1.7, −1.8; HR-MS: calcd for $C_{51}H_{90}O_8Si_3$ $[M+Cs]^+$ 1047.4999, found 1047.4970.

Luche reduction of ketone 52: A solution of ketone **52** (17.0 mg, 18.6 μmol) and $CeCl_3 \cdot 7H_2O$ (35 mg, 93 μmol) in THF/MeOH 1:1 (1.0 mL total) was cooled at −78 °C and treated with $LiBH_4$ (46 μL, 93 μmol, 2 M in THF). After stirring for 30 min, the mixture was allowed to warm to 25 °C and stirred for 3 h. The reaction mixture was diluted with aqueous saturated ammonium chloride (5 mL) and extracted with Et_2O (5 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (preparative silica gel plate, 15% Et_2O in hexanes) to afford a 3:1 mixture of diastereomeric alcohols **5** and **51** (combined amount: 13.8 mg, 15 μmol, 81%).

Acid 53: Succinic anhydride (12 mg, 120 μmol) and *N*-dimethylaminopyridine (17 mg, 144 μmol) were added to a solution of alcohol **5** (11 mg, 12 μmol) in CH_2Cl_2 (1 mL) and the reaction mixture was stirred 3 h at 25 °C. Upon completion of the reaction, the mixture was diluted with aqueous saturated ammonium chloride (5 mL) and extracted with CH_2Cl_2 (5 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on a preparative silica plate (2% MeOH in ethyl acetate) to yield acid **53** (10.3 mg, 10 μmol, 85%). **53**: colorless solid; R_f = 0.5 (10% methanol in CH_2Cl_2); $[\alpha]_D^{25}$: −19.7 (c = 0.12, CH_2Cl_2); IR (film): $\tilde{\nu}_{max}$ = 3409, 2960, 2923, 1716, 1648, 1470, 1248, 1156 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ = 7.60 (dd, 1H, J = 6.5, 15.5 Hz), 6.78 (d, 1H, J = 15.5 Hz), 6.70 (d, 1H, J = 16.0 Hz), 6.41 (dd, 1H, J = 4.5, 16.0 Hz), 6.26 (t, 1H, J = 6.5 Hz), 6.19 (d, 1H, J = 16.0 Hz), 6.17 (s, 1H), 5.91 (d, 1H, J = 3.5 Hz), 5.80 (dd, 1H, J = 16.0, 8.5 Hz), 4.60–4.58 (m, 1H), 4.29–4.18 (m, 4H), 3.60–3.56 (m, 1H), 2.79–2.55 (m, 5H), 2.40 (s, 3H), 2.38–2.04 (m, 3H) 1.81 (s, 3H), 1.76–1.58 (m, 6H), 1.39–1.21 (m, 8H), 1.17–1.02 (m, 22H), 0.95–0.82 (m, 10H), 0.73 (d, 3H, J = 7.0 Hz), −0.80 (s, 9H), −0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ = 171.5, 168.6, 167.0, 154.3, 151.5, 137.3, 135.5, 133.8, 131.3, 130.8, 127.5, 120.9, 120.8, 107.6, 88.0, 79.3, 78.3, 78.2, 62.7, 61.6, 44.7, 39.1, 34.8, 34.6, 34.5, 32.1, 31.9, 30.0, 29.9, 29.5, 25.7, 23.4, 18.3, 17.8, 17.5, 17.3, 14.2, 13.6, 12.7, 12.4, −1.7; HR-MS: calcd for $C_{55}H_{96}O_{11}Si_3$ $[M+Cs]^+$ 1149.5315, found 1149.5342.

Reveromycin B (4): A solution of acid **53** (3.1 mg, 3 μmol) in THF (0.1 mL) was treated with tetra-*n*-butylammonium fluoride (30 μL of a 1 M solution in THF, 30 μmol) at 25 °C for 2 h. The reaction mixture was then diluted with aqueous saturated ammonium chloride (2 mL), the pH was adjusted to 3 with dilute HCl and the mixture was extracted with ethyl acetate (5 × 5 mL). The organic layer was dried, concentrated, and purified by chromatography purified by chromatography on a preparative silica gel plate (10% MeOH in CH_2Cl_2) to yield reveromycin B (**4**) (1.4 mg, 2.1 μmol, 69%). **4**: white solid, R_f = 0.25 (15% methanol in CH_2Cl_2); $[\alpha]_D^{25}$: −61 (c = 0.1, MeOH); IR (film): $\tilde{\nu}_{max}$ = 3427, 2960, 2923, 2861, 1740, 1568, 1414, 1377, 1260, 1162 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ = 6.94 (dd, 1H, J = 15.6, 7.6 Hz), 6.38 (d, 1H, J = 15.6 Hz), 6.25 (d, 1H, J = 16.0 Hz), 6.19 (dd, 1H, J = 4.4, 16.0 Hz), 5.80 (d, 1H, J = 15.6 Hz), 5.78 (s, 1H), 5.75 (t, 1H, J = 6.8 Hz), 5.55 (d, 1H, J = 4.4 Hz), 5.50 (dd, 1H, J = 15.6, 7.6 Hz), 4.11 (m, 1H), 3.39 (m, 1H), 2.65–2.45 (m, 5H), 2.25–2.15 (m, 5H), 2.01–1.30 (m, 18H), 1.01 (d, 3H, J = 6.4 Hz), 0.91 (t, 3H, J = 7.2 Hz), 0.83 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ = 177.9, 173.4, 171.7, 171.1, 152.0, 151.3, 138.6, 136.3, 135.3, 132.0, 131.0, 127.5, 123.6, 122.7, 108.7, 88.9, 80.5, 78.7, 77.4, 44.2, 39.7, 35.9, 35.6, 35.4, 33.0, 32.9, 31.4, 30.8, 30.3, 26.7, 24.4, 18.3, 15.3, 14.7, 14.1, 12.9; HR-MS: calcd for $C_{36}H_{52}O_{11}$ $[M+Na]^+$ 683.3407, found 683.3388.

C19-*epi*-Reveromycin B (55): White solid, R_f = 0.20 (15% methanol in CH_2Cl_2); $[\alpha]_D^{25}$: −19 (c = 0.1, MeOH); IR (film): $\tilde{\nu}_{max}$ = 3429, 2959, 2928, 2861, 1740, 1566, 1410, 1377, 1260 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ = 6.85 (dd, 1H, J = 15.6, 7.6 Hz), 6.41 (d, 1H, J = 15.6 Hz), 6.30 (d, 1H, J = 16.0 Hz), 6.15 (dd, 1H, J = 5.2, 16.0 Hz), 5.89 (s, 1H), 5.85 (d, 1H, J = 14.8 Hz), 5.76 (t, 1H, J = 7.6 Hz), 5.56 (d, 1H, J = 6.0 Hz), 5.53 (dd, 1H, J = 15.2, 7.6 Hz), 4.11 (m, 1H), 3.55 (m, 1H), 2.65–2.45 (m, 6H), 2.25–2.15 (m, 4H), 2.01–1.30 (m, 18H), 1.01 (d, 3H, J = 6.4 Hz), 0.91 (t, 3H, J = 7.2 Hz), 0.83 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ = 178.0, 173.9, 173.8, 172.1, 171.6, 153.2, 152.0, 138.4, 137.7, 136.9, 130.6, 130.5, 127.7, 123.3, 122.2, 108.6, 88.9, 80.4, 78.1, 77.3, 44.0, 39.7, 35.6, 35.4, 35.3, 32.8, 31.5, 30.9, 30.3, 26.6, 24.7, 20.7, 18.1, 15.4, 14.2, 12.8; HR-MS: calcd for $C_{36}H_{52}O_{11}$ $[M+Na]^+$ 683.3407, found 683.3395.

Acknowledgement

Financial support from the Cancer Research Coordinating Committee, the UCSD Academic Senate, the American Cancer Society (IRG, RPG CDD-9922901), the NSF (Shared Instrumentation Grant CHE-9709183) and the Hellman Foundation (Faculty Research Fellowship to EAT) is gratefully acknowledged. We thank Professor H. Osada (RIKEN Institute, Japan) for providing us with the NMR data of natural reveromycin B and for stimulating discussions. We kindly thank David M. Remick, Donald A. Watson and Hung V. Tran for their contributions to this project. We also thank Professor M. Goodman (UCSD, Department of Chemistry and Biochemistry) for allowing us access to his polarimeter and IR instruments and Professor D. John Faulkner (Scripps Institute of Oceanography) for critical suggestions on the reported NOE assignments.

[1] For a preliminary communication on the synthesis of **4**, see: K. E. Drouet, E. A. Theodorakis, *J. Am. Chem. Soc.* **1999**, *121*, 456–457.

[2] For recent reviews on this topic see: a) *Growth Factors and Receptors: A Practical Approach* (Eds.: I. A. McCay, K. D. Brown), University Press, New York, **1998**; b) *Growth Factors and Signal Transduction in Development* (Ed.: M. Nilsen-Hamilton), Wiley-Liss, NY, **1994**; c) *Growth Factors, Peptides and Receptors* (Ed.: T. W. Moody), Plenum Press, New York, **1993**; d) V. Sorrentino, *Anticancer Res.* **1989**, *9*, 1925–1936; e) N. W. Merrall, R. Plevin, G. W. Gould, *Cellular Signalling* **1993**, *5*, 667–675; f) D. T. Hung, T. F. Jamison, S. L. Schreiber, *Chem. Biol.* **1996**, *3*, 623–639.

[3] a) D. J. R. Laurence, B. A. Gusterson, *Tumor Biol.* **1990**, *11*, 229–261; b) L. C. Groenen, E. C. Nice, A. W. Burgess, *Growth Factors* **1994**, *11*,

235 – 257; c) M. Baron, D. G. Norman, T. S. Harvey, P. A. Handford, M. Mayhew, A. G. D. Tse, G. G. Brownlee, I. D. Campbel, *Protein Sci.* **1992**, *1*, 81 – 90.

[4] a) T. Yamuchi, K. Ueki, K. Tobe, H. Tamemoto, N. Sekine, M. Wada, M. Honjo, M. Takahashi, T. Takahashi, H. Hirai, T. Tushima, Y. Akanuma, T. Fujita, I. Komuro, Y. Yazaki, T. Kadawaki, *Nature* **1997**, *390*, 91 – 96; b) B. Margolis, S. G. Rhee, S. Felder, M. Mervic, R. Lyall, A. Levitzki, A. Ullrich, A. Zilberstein, J. Schlessinger, *Cell* **1989**, *57*, 1101 – 1107.

[5] a) K. Yoshida, E. Kyo, T. Tsuda, T. Tsujino, M. Ito, M. Niimoto, E. Tahara, *Int. J. Cancer* **1990**, *45*, 131 – 135; b) M. E. Stearns, M. Stearns, *Cancer Metastasis Rev.* **1993**, *12*, 39 – 52; c) J. G. M. Klijn, P. M. J. J. Berns, P. I. M. Schmitz, J. A. Foekens, *Endocrine Rev.* **1992**, *13*, 3 – 17; d) H. Modjtahedi, C. Dean, *Int. J. Oncol.* **1994**, *4*, 277 – 296; e) M. B. Sporn, A. B. Roberts, *Nature* **1985**, *313*, 745 – 747; f) A. S. Goustin, E. B. Leof, G. D. Shipley, H. L. Moses, *Cancer Res.* **1986**, *46*, 1015 – 1029.

[6] a) H. Koshino, H. Takahashi, H. Osada, K. Isono, *J. Antibiot.* **1992**, *45*, 1420 – 1427; b) H. Takahashi, H. Osada, H. Koshino, T. Kudo, S. Amano, S. Shimizu, M. Yoshihama, K. Isono, *J. Antibiot.* **1992**, *45*, 1409 – 1413; c) H. Osada, H. Koshino K. Isono, H. Takahashi, G. Kawanishi, *J. Antibiot.* **1991**, *44*, 259 – 261.

[7] a) H. Takahashi, H. Osada, H. Koshino, M. Sasaki, R. Onose, M. Nakakoshi, M. Yoshihama, K. Isono, *J. Antibiot.* **1992**, *45*, 1414 – 1419; b) H. Takahashi, Y. Yamashita, H. Takaoka, J. Nakamura, M. Yoshihama, H. Osada, *Oncology Res.* **1997**, *9*, 7 – 11.

[8] M. Ubukata, H. Koshino, H. Osada, K. Isono, *J. Chem. Soc. Chem. Commun.* **1994**, 1877 – 1878.

[9] a) T. Shimizu, R. Kobayashi, K. Osako, H. Osada, T. Nakata, *Tetrahedron Lett.* **1996**, *37*, 6755 – 6758; b) K. J. McRae, M. A. Rizzacasa, *J. Org. Chem.* **1997**, *62*, 1196 – 1197; c) K. D. Drouet, T. Ling, H. V. Tran, E. A. Theodorakis, *Org. Lett.* **2000**, *2*, 207 – 210.

[10] For a recent review on spiroketals see: F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617 – 1661.

[11] In our recently communicated synthesis of **4** we abbreviated the $Me_3SiCH_2CH_2$- group as SEM. Since SEM usually refers to $Me_3SiCH_2CH_2OCH_2$-, we are using TMSE as the abbreviation herein. We thank Professor B. H. Lipshutz for bringing to our attention this oversight.

[12] For selected references on the Kishi – Nozaki (Nozaki – Hiyama – Kishi) reaction see: a) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 2533 – 2534; b) P. Cintas, *Synthesis* **1992**, 248 – 257; c) H. Jin, J. Uenishi, W. J. Christ, Y. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644 – 5646; d) P. Wipf, S. Lim, *J. Chem. Soc. Chem. Commun.* **1993**, 1654 – 1656; e) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048 – 6050; f) Y. Kishi, *Pure Appl. Chem.* **1992**, *64*, 343 – 350; g) Y. Kishi, *Pure Appl. Chem.* **1989**, *61*, 313 – 324; h) C. Chen, K. Tagami, Y. Kishi, *J. Org. Chem.* **1995**, *60*, 5386 – 5387; i) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349 – 12357.

[13] a) G. C. Andrews, T. C. Crawford, B. E. Bacon, *J. Org. Chem.* **1981**, *46*, 2976 – 2977; b) C. R. Schmid, D. A. Bradley, *Synthesis* **1992**, 587 – 590.

[14] For selected reviews on this topic see: a) J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron* **1986**, *42*, 447 – 488; b) M. T. Reetz, *Acc. Chem. Res.* **1993**, *26*, 462 – 468; c) M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542 – 558; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556 – 569.

[15] a) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, D. vanDerveer, *J. Org. Chem.* **1980**, *45*, 3846 – 3856; b) H. Nagano, M. Ohno, Y. Miyamae, Y. Kuno, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2814 – 2820; c) H. Nagano, M. Ohno, Y. Miyamae, *Chem. Lett.* **1990**, 463 – 466; d) W. C. Still, J. H. McDonald, *Tetrahedron Lett.* **1980**, *21*, 1031 – 1034; e) W. C. Still, J. A. Schneider, *Tetrahedron Lett.* **1980**, *21*, 1035 – 1038; f) H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1986**, *51*, 3769 – 3771.

[16] a) D. Enders, J. Tiebes, N. De Kimpe, M. Keppens, C. Stevens, G. Smagghe, O. Betz, *J. Org. Chem.* **1993**, *58*, 4881 – 4884; b) D. Enders, W. Gatzweiler, U. Jegelka, *Synthesis* **1991**, 1137 – 1141; c) D. Enders, *Asymmetric Synthesis* **1984**, *3*, 275 – 339.

[17] H. C. Brown, P. K. Jadhav, B. Singram, *Mod. Synth. Meth.* **1986**, *4*, 307 – 356.

[18] SAMP hydrazine was prepared according to the literature procedure: D. Enders, P. Fey, H. Kipphard, *Org. Synth.* **1987**, *65*, 173 – 182.

[19] a) P. J. Garegg, B. Samuelson, *J. Chem. Soc. Perkin Trans. I* **1980**, 2866 – 2869; b) J. A. Marshall, D. G. Cleary, *J. Org. Chem.* **1986**, *51*, 858 – 863.

[20] H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919 – 5923.

[21] a) A. B. Jones, M. Yamaguchi, A. Patten, S. J. Danishefsky, J. A. Ragan, D. B. Smith, S. L. Schreiber, *J. Org. Chem.* **1989**, *54*, 19 – 20; b) M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Ueling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583 – 5601.

[22] a) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287; b) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899.

[23] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, 3769 – 3772.

[24] J. M. Humphrey, J. B. Eggen, A. R. Chamberlin, *J. Am. Chem. Soc.* **1996**, *118*, 11759—11770.

[25] For selected reviews on palladium-catalyzed transformations see: a) J. Tsuji, *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, Wiley, New York, **1997**; b) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**; c) T. N. Mitchell, *Synthesis* **1992**, 803 – 815; d) V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73 – 78; e) V. Farina, V. Krishnamurthy, W. J. Scott, *Organic Reactions*, *Vol. 50* (Ed.: L. A. Paquette), Wiley, New York, **1997**, pp. 1 – 652.

[26] a) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737 – 1739; b) D. A. Evans, A. S. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 11323—11324.

[27] a) A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, 4171 – 4174; b) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815 – 3818; c) D. L. Clark, C. H. Heathcock, *J. Org. Chem.* **1993**, *58*, 5878 – 5879.

[28] H. X. Zhang, F. Guibe, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857 – 1867.

[29] A. B. Smith III, G. R. Ott, *J. Am. Chem. Soc.* **1998**, *120*, 3935 – 3948.

[30] a) J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, *109*, 813 – 817; b) C. Mateo, D. J. Cardenas, C. Fernandez-Rivas, A. M. Echavarren, *Chem. Eur. J.* **1996**, *2*, 1596 – 1606; c) A. L. Casado, P. Espinet, *J. Am. Chem. Soc.* **1998**, *120*, 8978 – 8985.

[31] D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679 – 680

[32] For selected impressive examples on the use of Stille coupling in natural products synthesis see: a) M. B. Andrus, S. D. Lepore, *J. Am. Chem. Soc.* **1997**, *119*, 2327 – 2328; b) A. B. Smith III, G. R. Ott, *J. Am. Chem. Soc.* **1996**, *118*, 13095 – 13096; c) D. A. Evans, J. S. Johnson, *J. Org. Chem.* **1997**, *62*, 786 – 787; d) A. B. Smith III, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, B. A. Salvatore, *J. Am. Chem. Soc.* **1997**, *119*, 10935 – 10946; e) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, *115*, 4419 – 4420; f) K. C. Nicolaou, N. Winssinger, J. Pastor, F. Murphy, *Angew. Chem.* **1998**, *110*, 2677 – 2680; *Angew. Chem. Int. Ed.* **1998**, *37*, 2534 – 2537; g) T. M Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3164 – 3166; *Angew. Chem. Int. Ed.* **1998**, *37*, 2993 – 2995; h) T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3166 – 3168; *Angew. Chem. Int. Ed.* **1998**, *37*, 2995 – 2998.

[33] D. A. Evans, J. R. Gage, J. L. Leighton, *J. Am. Chem. Soc.* **1992**, *114*, 9434 – 9453.

[34] a) L. S. Liebeskind, R. W. Fengl, *J. Org. Chem.* **1990**, *55*, 5359 – 5364; b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 5905 – 5911.

[35] a) E. Negishi, N. Okukado, A. O. King, D. E. Van Horn, B. I. Spiegel, *J. Am. Chem. Soc.* **1978**, *100*, 2254 – 2256; b) D. E. Van Horn, E. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252 – 2254.

[36] For selected recent synthetic applications of Negishi coupling see: a) B. H. Lipshutz, C. Lindsey, *J. Am. Chem. Soc.* **1997**, *119*, 4555 – 4556; b) A. Palmgren, A. Thorarensen, J. E. Backvall, *J. Org. Chem.* **1998**, *63*, 3764 – 3768; c) G. Boche, M. Klein, *Synthesis* **1999**, 1246 – 1250; d) M. Jorgensen, M. Larsen, *J. Org. Chem.* **1997**, *62*, 4171 – 4173.

[37] a) J. S. Panek, T. Hu, *J. Org. Chem.* **1997**, *62*, 4912 – 4913; b) J. S. Panek, T. Hu, *J. Org. Chem.* **1997**, *62*, 4914 – 4915; c) J. S. Panek, T. Hu, *J. Org. Chem.* **1997**, *64*, 3000 – 3001.

[38] For alternative, yet more tedious, approaches to this type of conjugated dienes see: a) A. R. de Lera, A. Torrado, B. Inglesias, S. Lopez, *Tetrahedron Lett.* **1992**, *33*, 6205 – 6208; b) J. P. Genet, A. Linquist, E. Blart, V. Mouries, M. Savignac, M. Vaultier, *Tetrahedron Lett.* **1995**, *36*, 1443 – 1446.

0947-6539/00/0611-2000 $ 17.50+.50/0

[39] For recent impressive demonstrations of the application of the Kishi–Nozaki coupling to natural products synthesis see: a) J. A. McCauley, K. Nagasawa, P. A. Lander, S. G. Mischke, M. A. Semones, Y. Kishi, *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648; b) X.-T. Chen, S. K. Bhattacharya, B. Zhou, C. E. Gutteridge, T. R. R. Pettus, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579; c) M. M. Victor, R. A. Pilli, *Tetrahedron Lett.* **1998**, *39*, 4421–4424.
[40] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
[41] a) P. Sieber, *Helv. Chim. Acta* **1977**, *60*, 2711–2716; b) B. H. Lipshutz, T. A. Miller, *Tetrahedron Lett*. **1989**, *30*, 7149–7152.
[42] Formation of a putative [6,6]spiroketal ring was monitored by ^{13}C NMR. The C15 spiroketal center of **1** resonates at about $\delta = 95$ (indicative of a [6,6]spiroketal ring), while the C15 center of **4** resonates at about $\delta = 109$ (indicative of a [5,6]spiroketal ring).
[43] A second independent synthesis of reveromycin B (**4**) has been recently reported: T. Masuda, K. Osako, T. Shimizu, T. Nakata, *Org. Lett.* **1999**, *1*, 941–944.
[44] Since the submission of this manuscript a third total synthesis of reveromycin B (**4**) has been reported: A. N. Cuzzupe, C. A. Hutton, M. J. Lilly, R. K. Mann, M. A. Rizzacasa, S. C. Zammit, *Org. Lett.* **2000**, *2*, 191–194.

Received: November 15, 1999 [F2142]