Total Synthesis

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Total Synthesis of the Potent Antitumor Macrolides Pladienolide B and D**

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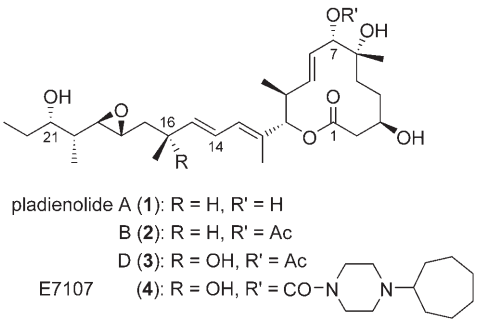
In 2004 Sakai et al. reported the identification of seven 12-membered macrolides (pladienolides A–G), from *Streptomyces platensis* Mer-11107 by way of a cell-based assay that evaluated the suppression of hypoxia-induced gene expression controlled by the human VEGF promoter.[1] The most potent pladienolides (B (**2**) and D (**3**)) have IC_{50} values in the low nanomolar range (Scheme 1). They also inhibit the growth of a variety of cancer cell lines in vitro with low nanomolar IC_{50} values. COMPARE analysis with panel screening of 39 human cancer cell lines indicated that the compounds have a unique mode of antitumor action unlike those of anticancer drugs currently in clinical use.[2] Pladienolides B and D also cause in vivo tumor regression in several human cancer xenograft models.[2] These results encouraged us to search for novel antitumor agents based on these unique lead compounds. After intensive studies, we discovered E7107 (**4**), a urethane derivative of pladienolide D that possesses enhanced in vivo potency and better physicochemical properties.[3] Intravenous treatment of several tumor xenograft models with E7107 for five consecutive days has led to complete remission as well as tumor shrinkage in a variety of tumor xenografts.[4] In light of these promising preclinical data, E7107 will soon enter clinical trials.



Scheme 1. Pladienolides A, B, and D as well as E7107.

The absolute structure of pladienolide B was recently elucidated by Asai et al.[5] To verify this structure, and that of pladienolide D, and to facilitate the discovery of novel analogues with advantageous pharmaceutical profiles we have executed the first total syntheses of pladienolides B and D. Our syntheses confirm the absolute structures of the compounds and provide a strategy for the preparation of novel synthetic analogues based on the efficient application of olefin metathesis technology.

Our retrosynthetic analysis is shown in Scheme 2. We wanted to install the stereogenic centers in a reagent-controlled fashion so that we could synthesize other stereoisomers simply by changing the stereochemistry of the reagents. The C14–C15 double bond was disconnected to afford a side-chain moiety and a macrolide unit; this strategy gave us efficient access to structural variants of each moiety. Our knowledge of the reactivity of the hydroxy groups of pladienolide A (**1**) led us to believe that the C7 hydroxy group could be acetylated regioselectively. We expected to be able to obtain the macrolide moiety by an esterification reaction and a subsequent ring-closing olefin metathesis (RCM) between a C1–C8 unit and a C9–C14 unit.[6] To our knowledge, there have been only a few reported uses of RCM for the construction of an aliphatic (not containing phenyl moieties as ring members) 12-membered macrolide structure, but there is no precedent for sterically hindered and highly functionalized ones.[7] We expected to be able to prepare the side-chain moiety by means of a Julia–Kocienski olefination[8] and the asymmetric epoxidation developed by Shi and coworkers[9] from a C15–C18 unit and a C19–C23 unit.

Our syntheses commenced with the construction of the macrolide moiety (Scheme 3). Aldehyde **5**, prepared from nerol by protection with a PMB group and regioselective ozonolysis,[10] was subjected to the Sm^{II}-mediated asymmetric Reformatsky reaction described by Fukuzawa et al. using bromoacetyloxazolidinone **6** as a chiral auxiliary to afford β-hydroxyamide **7** with good diastereoselectivity (82% *de*).[11]

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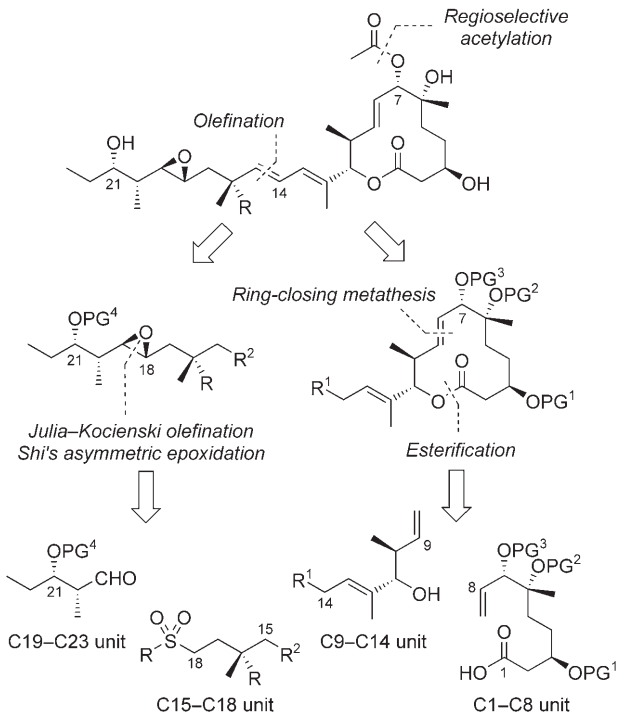
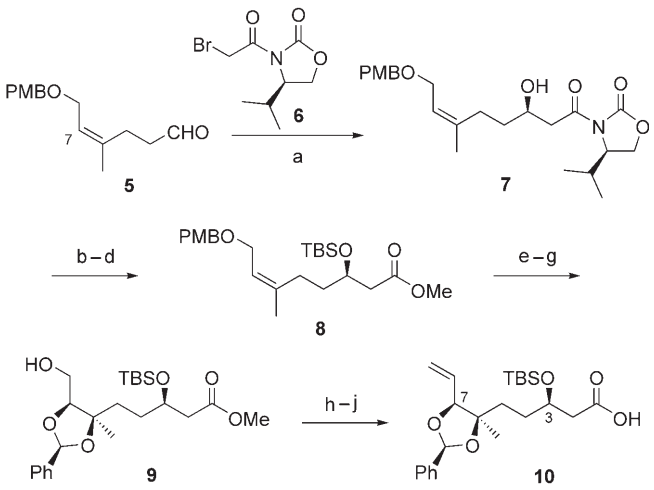


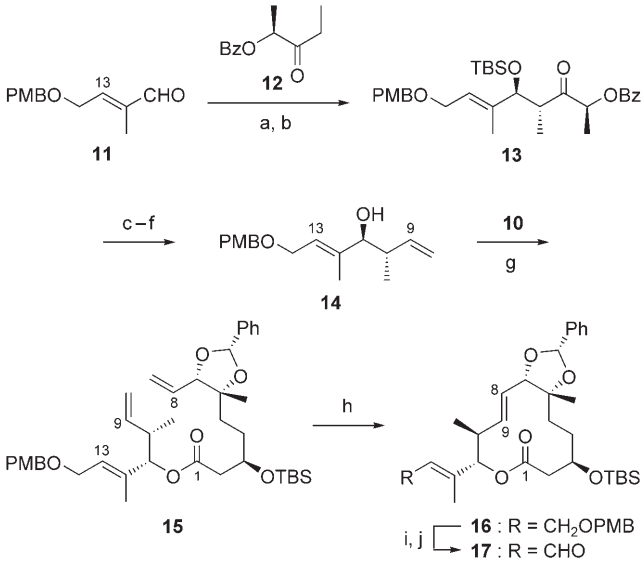
Scheme 2. Retrosynthetic analysis of pladienolides. PG = protecting group.



Scheme 3. Synthesis of C1–C8 unit **10**: a) Sm^0, CH_2I_2, **6**, THF, −78 °C to RT, 90% (>98% *de*); b) LiOH, H_2O_2, THF/H_2O (4:1), RT; c) TMS diazomethane, THF/MeOH (10:1), RT; d) TBSCl, imidazole, DMF, RT, 85% (3 steps); e) AD-mix-α, methanesulfonamide, *t*BuOH/H_2O (1:1), 0 °C, 92% (76% *de*); f) benzaldehyde dimethyl acetal, PPTS, CH_2Cl_2, RT, 98%; g) DDQ, CH_2Cl_2/H_2O (10:1), 0 °C, recrystallization, 65%; h) DMP, CH_2Cl_2, RT; i) methyltriphenylphosphonium iodide, *n*BuLi, THF, −15 °C to RT, 78% (2 steps); j) LiOH, THF/MeOH/H_2O (2:2:1), RT, 82%. PMB = *p*-methoxybenzyl, *de* = diastereomeric excess, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, PPTS = pyridinium *p*-toluenesulfonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane.

Separation of the diastereomers by column chromatography on silica gel gave the desired β-hydroxyamide **7** in >98% *de*. After removal of the chiral auxiliary, protection of the hydroxy group, and methylation, ester **8** was obtained in good yield (85%).[12] A second asymmetric reaction, the asymmetric dihydroxylation of **8**, proceeded in 76% *de*, but the resulting isomers could not be separated.[12] Protection of the diastereomeric mixture of *syn*-diols with a benzylidene acetal group and subsequent removal of the terminal PMB group afforded primary alcohol **9** as a crystalline solid. Recrystallization afforded **9** as a single diastereomer.[13] Sequential oxidation, Wittig olefination, and hydrolysis gave the desired C1–C8 unit **10** in 64% yield (Scheme 3).

Synthesis of the C9–C14 unit began with construction of the C10 and C11 stereogenic centers by an *anti*-aldol reaction developed by Paterson et al. by using aldehyde **11** and lactate-derived chiral ketone **12** (Scheme 4).[14] This reaction proceeded with excellent diastereoselectivity (98% *de*), and the desired *anti*-aldol product **13** was obtained in pure form after recrystallization and protection with a TBS group. An additional four steps, including oxidative cleavage of the α-benzoyloxy ketone, gave desired C9–C14 unit **14**. An esterification reaction between C1–C8 unit **10** and C9–C14 unit **14** by means of the method described by Yamaguchi and co-workers afforded bis-terminal olefin **15**.[15]



Scheme 4. Synthesis of C9–C14 unit **14** and macrolide moiety **17**: a) **12**, Cy_2BCl, Me_2NEt, diethyl ether, −78 °C to −26 °C, recrystallization, 81% (>99% *de*); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, quant.; c) $LiBH_4$, THF, −78 °C to RT; d) $NaIO_4$, THF/H_2O (4:1), RT; e) methyltriphenylphosphonium iodide, *n*BuLi, THF, −15 °C, 73% (3 steps); f) 1 N HCl, MeCN, RT, 99%; g) **10**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 °C to RT, then **14**, DMAP, toluene, RT, 93%; h) 2nd-generation Hoveyda–Grubbs catalyst, BHT, toluene, reflux, 46%; i) DDQ, CH_2Cl_2/pH 7 buffer (10:1), RT, 80%; j) DMP, CH_2Cl_2, RT, quant.; Bz = benzoyl, Cy = cyclohexyl, Tf = trifluoromethanesulfonyl, DMAP = 4-dimethylaminopyridine, 2nd generation Hoveyda–Grubbs catalyst = [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro[*O*-isopropoxyphenylmethylidene]ruthenium, BHT = 2,6-di-*tert*-butyl-4-methylphenol.

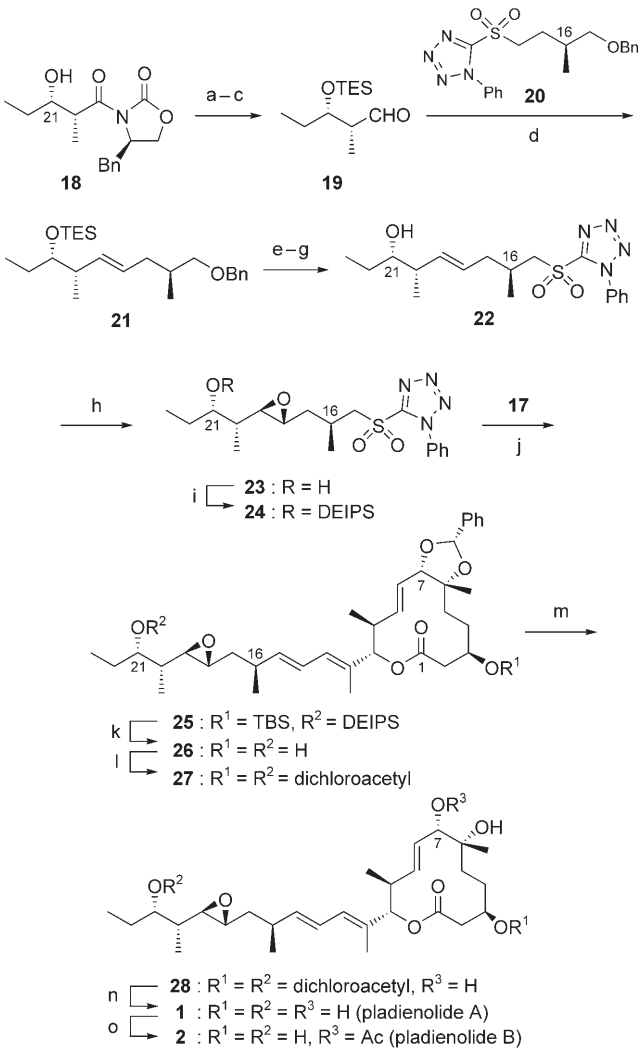
We next investigated the key RCM reaction to construct the macrolide moiety. By screening various reaction con-

ditions (catalysts, solvents, additives, reaction temperatures, etc.)[16,17] we determined that the use of the second-generation Hoveyda–Grubbs catalyst in refluxing toluene afforded the best results: the desired macrolide **16** was obtained in 46% yield.[16d] Steric hindrance was clearly responsible for the low yield. A substantial amount of isomerized product with a C7–C8 olefin was also formed.[18] Removal of the PMB group and subsequent oxidation with DMP gave macrolide **17** for coupling with the side-chain moiety. The macrolide **16** was obtained as a crystalline solid, and its three-dimensional structure, including the absolute configuration, was confirmed by X-ray crystallographic analysis.

Next, we synthesized the side-chain moiety of pladienolide B (Scheme 5). Aldehyde **19** was obtained from the known hydroxy amide **18**.[19] Aldehyde **19** was treated with the C15–C18 unit (sulfone **20**), which was prepared in six steps from methyl (*R*)-3-hydroxy isobutyrate according to a standard procedure,[20] to give *trans*-olefin **21** exclusively. After removal of the Bn group, the resulting alcohol was converted into sulfone **22** with concurrent removal of the TES group during the oxidation step. The unprotected hydroxy group was found to increase the yield and diastereoselectivity of the asymmetric epoxidation described by Shi and co-workers,[21] and afforded desired epoxide **23** in good yield as a single diastereomer after recrystallization.[9] The structure and stereochemistry of **23** were confirmed by X-ray crystallographic analysis. The hydroxy group of **23** was protected as the DEIPS ether to provide side-chain fragment **24**.

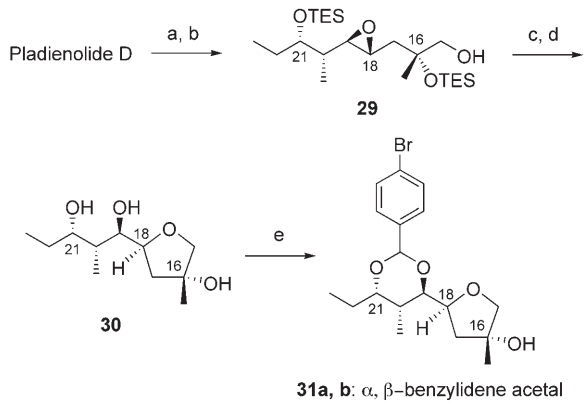
With the macrolide and the side-chain fragments in hand, we investigated their coupling to construct the entire carbon framework of pladienolide B. Julia–Kocienski olefination between aldehyde **17** and sulfone **24** smoothly afforded the desired *E*,*E*-diene **25** exclusively. We expected to be able to remove all the protecting groups from **25** in a single step under acidic conditions to afford tetraol **1** (pladienolide A), but the benzylidene group proved resistant under the acidic conditions tested; the two silyl groups were removed before the benzylidene group, and the resulting hydroxy group at the C21-position opened the neighboring epoxide to form a tetrahydrofuran ring. Therefore, the two silyl groups were converted into acid-stable dichloroacetyl groups to provide **27**. Note that when an acetyl group was used instead of the dichloroacetyl group, the carbonyl unit of the acetyl moiety on the C21-hydroxy group also attacked the epoxide by means of a neighboring effect, and two diols were obtained.[22] Therefore, the dichloroacetyl group, in which the carbonyl oxygen atom is relatively electron-deficient, was the best choice in this case. The benzylidene group was removed by treatment with PPTS in MeOH over 46 h to afford 6,7-diol **28**. Methanolysis of **28** gave pladienolide A (**1**). The final regioselective acetylation proceeded as expected, and pladienolide B (**2**) was obtained in good yield. The spectral data and optical rotation data of **1** and **2** were in agreement with the data available for natural pladienolides A and B, respectively.[23]

We next approached the total synthesis of pladienolide D. Pladienolides B and D differ only at C16, where a hydroxy group is present in pladienolide D but not in pladienolide B. Similarities in the ^{1}H and ^{13}C NMR spectra suggested that

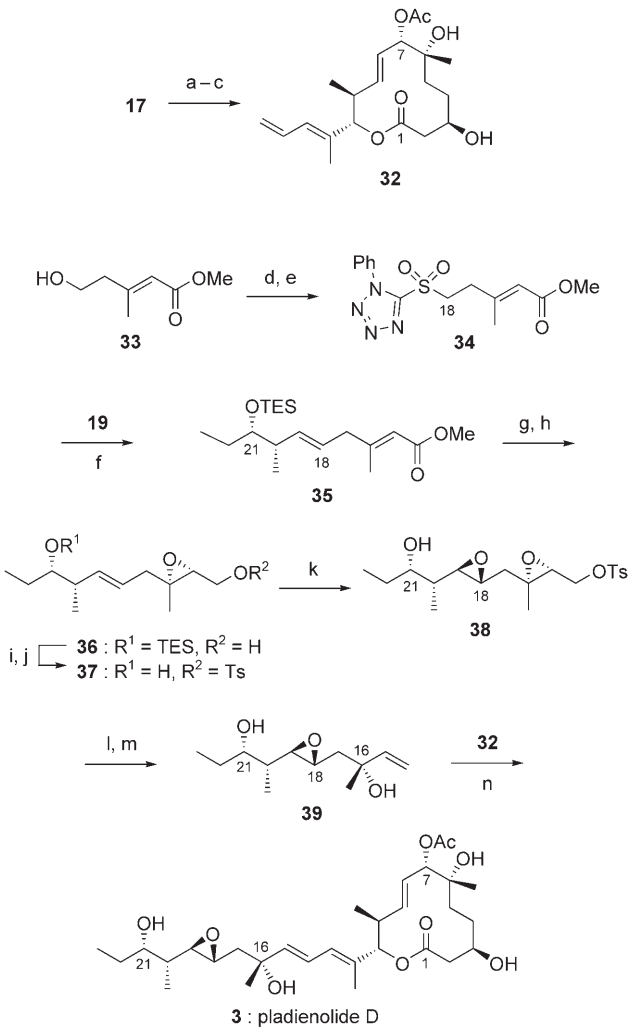


Scheme 5. Synthesis of side-chain moiety **24** and completion of the total syntheses of pladienolides A and B: a) *N*,*O*-dimethylhydroxylamine hydrochloride, Me_3Al, CH_2Cl_2, −78 °C, quant.; b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%; c) DIBAL, toluene, −78 °C, 89%; d) **20**, KHMDS, THF, −78 °C, 68%; e) Li^0, 4,4′-di-*tert*-butyl-biphenyl, THF, −78 °C, 77%; f) 5-mercapto-1-phenyltetrazole, Ph_3P, DIAD, THF, RT, 91%; g) $MoO_7(NH_4)_6{\cdot}4H_2O$, H_2O_2, EtOH, RT, 81%; h) 1,2:4,5-di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose, oxone, K_2CO_3, MeCN/0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 0.4 mM Na_2EDTA (pH 9; 3:2), 0 °C, recrystallization, 71% (>99% *de*); i) DEIPSCl, imidazole, DMF, RT, quant.; j) **17**, KHMDS, THF, −78 °C, 64%; k) TBAF, THF, RT, quant.; l) dichloroacetic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C, quant.; m) PPTS, MeOH, RT, 64%; n) K_2CO_3, MeOH, RT, 96%; o) acetic anhydride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 82%. TES = triethylsilyl, DIBAL = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazide, Bn = benzyl, DIAD = diisopropyl azodicarboxylate, EDTA = ethylenediaminetetraacetic acid, DEIPS = diethylisopropylsilyl, TBAF = tetrabutylammonium fluoride.

pladienolide D has the same stereochemistry as pladienolide B at the other nine stereogenic carbon centers. However, because C16 is quaternary, *J*-based configuration analysis of pladienolide D cannot be used to elucidate the stereochemistry at that position. To address this issue, we carried out a chemical degradation and derivatization study on pladienolide D (Scheme 6). The side-chain fragment bearing the C16



Scheme 6. Chemical degradation of pladienolide D and derivatization of alcohol **29** to benzylidene acetal **31**: a) TESCl, Et_3N, DMAP, CH_2Cl_2, RT, 82%; b) O_3, dimethylsulfide, CH_2Cl_2/MeOH (1:1), −78°C, then $NaBH_4$, 0°C, 38%; c) TBAF, THF, RT, 89%; d) *t*BuOK, MeOH, RT, 73%; e) *p*-bromobenzaldehyde dimethyl acetal, CSA, CH_2Cl_2, RT, **31a** = 54%, **31b** = 28%. CSA = camphorsulfonic acid.



Scheme 7. Total synthesis of pladienolide D: a) Tebbe reagent, pyridine, toluene/THF (7:1), RT, 75%; b) PPTS, MeOH, RT, 77%; c) acetic anhydride, Et_3N, DMAP, CH_2Cl_2, RT, 93%; d) 5-mercapto-1-phenyltetrazole, Ph_3P, DIAD, THF, RT, quant.; e) $MoO_7(NH_4)_6{\cdot}4H_2O$, H_2O_2, EtOH, RT, quant.; f) KHMDS, **19**, DME/THF, −60°C, 97%; g) DIBAL, toluene, −78°C, 74%; h) $Ti(OiPr)_4$, (−)-DET, *t*BuOOH, 4-Å MS, −30°C, CH_2Cl_2, 91% (90% *de*); i) TsCl, Et_3N, DMAP, CH_2Cl_2, RT, quant.; j) 1 N HCl, THF, RT, quant.; k) 1,2:4,5-di-*O*-isopropylidene-D-erythro-2,3-hexodiuro-2,6-pyranose, oxone, K_2CO_3, MeCN/aqueous Na_2EDTA (4×10^{-4} M; 3:2), 0°C, 87% (81% *de*), then recrystallization, 52% (>99% *de*); l) KI, acetone-DMF, (5:1), reflux; m) Zn, CuI, EtOH/H_2O (2:3), sonication, RT (99% in 2 steps); n) **39**/**32** = 2/1, 2nd generation Grubbs catalyst (5 mol%), CH_2Cl_2, reflux, 64%. Tebbe reagent = [μ-chloro-μ-methylene[bis(cyclopentadienyl)titanium]dimethylaluminum], DME = 1,2-dimethoxyethane, DET = diethyl tartrate, Ts = *p*-toluenesulfonyl, 2nd-generation Grubbs catalyst = benzylidene-[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium.

stereogenic center (**29**) was prepared from natural pladienolide D (**3**) by protection with a TES group, careful ozonolysis, and reduction with $NaBH_4$.[24] Fragment **29** was deprotected with TBAF and then transformed to tetrahydrofuran **30** by treatment with potassium *tert*-butoxide. The 1,3-diol moiety of **30** was converted into the corresponding benzylidene acetal to afford **31** as a mixture of diastereomers (α:β 2:1), which were easily separated by column chromatography on silica gel. Compounds **31a** and **31b** were studied by extensive NMR analysis, and NOESY correlations observed for **31a** and **31b** supported the assignment of the stereochemistry of C16 as *R*, as shown in Scheme 1.[25]

By using the information obtained for the stereochemistry of pladienolide D, we started its total synthesis. We originally envisioned the use of a Julia–Kocienski olefination for coupling the macrolide and the side chain, as for pladienolide B. However, model reactions demonstrated that protection of the tertiary alcohol at C16 with TES, MOM, ethoxy ethyl, or SEM groups obstructed the Julia–Kocienski olefination. Therefore, olefin cross-metathesis (CM) seemed to be a better alternative to establish a quaternary carbon atom adjacent to the diene moiety in the side chain.[26] The CM reaction between the macrolide moiety bearing a terminal diene (**32**) and various tertiary allylic alcohols afforded products in good yield with the C16 quaternary carbon atom. Therefore, we used this key reaction in our synthesis.

The total synthesis of pladienolide D is shown in Scheme 7. Compound **32** was conveniently prepared from aldehyde **17**: sequential Tebbe olefination,[27] removal of the TBS and benzylidene acetal groups, and regioselective acetylation gave desired diene **32** in 54% overall yield from **17**. The side chain with a tertiary allyl alcohol moiety was prepared from known alcohol **33**.[28] Sulfone **34** was prepared in excellent yield from alcohol **33** by a Mitsunobu reaction[29] and subsequent oxidation.[30] Sulfone **34** was then allowed to react with aldehyde **19** to give skipped diene ester **35** in 97% yield and high *E* selectivity (*E*:*Z* 17:1).[8] Reduction of ester **35** with DIBAL gave the corresponding allyl alcohol, which was subjected to Sharpless asymmetric epoxidation[31] to afford epoxide **36** in good yield and diasteroselectivity (91%, 90% *de*). Tosylation of the primary hydroxy group and removal of the TES group under weakly acidic conditions provided alcohol **37**. Asymmetric epoxidation of **37** by the method developed by Shi and co-workers afforded diepoxide **38** (81% *de*), which was purified by recrystallization to give

optically pure **38**. Iodination and subsequent cleavage of the epoxide in **38** with a zinc/copper couple[32] gave desired tertiary allyl alcohol **39** in 99% yield. Finally, olefin cross-metathesis between **32** and **39** afforded pladienolide D (**3**) in 64% yield and excellent stereoselectivity.[26] The *E* selectivity was consistent with a literature report indicating that a CM reaction between an unprotected tertiary allylic alcohol and an α-olefin gives the *trans* olefin selectively.[26,33] In addition, Hoye and Zhao have reported that a free allylic hydroxy group has an activating effect on ring-closing metathesis (RCM).[34] Hence, the same effect may be a good driving force in our synthesis. It should also be noted that few examples of CM reactions between olefins bearing a quaternary carbon atom and an α-olefin during the synthesis of a natural product have been reported to the best of our knowledge.

The spectral data and optical rotation data of **3** were virtually identical to those of the natural product. We also compared the antitumor activity of synthetic pladienolides B and D with the activity of the natural products. The IC_{50} values of synthetic and natural pladienolides B and D against WiDr colon cancer cell growth inhibition were essentially identical: 0.90 nM and 7.5 nM for the synthetic products and 0.86 nM and 5.9 nM for the natural ones, respectively.

In conclusion, we have achieved the first total synthesis of pladienolides B (**2**) and D (**3**), through longest linear sequences of 22 and 19 steps, respectively, in overall yields of 2.1% and 2.2%, respectively. These syntheses confirmed the absolute stereochemistry of pladienolides B and D. Note that our synthetic approaches involve the first example of ring-closing metathesis for the construction of a sterically hindered aliphatic 12-membered macrolide structure and also exhibit an effective application of cross-metathesis to the synthesis of natural products. The exploitation of cross-metathesis at the culmination of our total synthesis is quite efficient and versatile because the fragments can be assembled without protecting groups to directly provide the final target in sufficient yield. We believe that this synthetic effort provides a practical route to novel pladienolide analogues that could not be obtained from natural resources.

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[1] a) T. Sakai, T. Sameshima, M. Matsufuji, N. Kawamura, K. Dobashi, Y. Mizui, *J. Antibiot.* **2004**, *57*, 173–179; b) T. Sakai, N. Asai, A. Okuda, N. Kawamura, Y. Mizui, *J. Antibiot.* **2004**, *57*, 180–187.

[2] Y. Mizui, T. Sakai, M. Iwata, T. Uenaka, K. Okamoto, H. Shimizu, T. Yamori, K. Yoshimatsu, M. Asada, *J. Antibiot.* **2004**, *57*, 188–196.

[3] a) Y. Kotake et al., see Supporting Information; b) J. Niijima et al., see the Supporting Information; c) Y. Kotake, J. Niijima, Y. Fukuda, M. Nagai, R. M. Kanada, T. Nakashima, M. Yoshida, T. Tsuchida (Mercian Corp., Eisai Co., Ltd), WO/2003/099813, **2003**.

[4] M. Iwata et al., see the Supporting Information.

[5] N. Asai, Y. Kotake, N. Fukuda, J. Niijima, T. Uehara, T. Sakai, *J. Antibiot.*, submitted.

[6] For recent reviews of ring-closing metathesis, see a) S.-Y. Han, S. Chang in *Handbook of Metathesis*, *Vol. 2* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, pp. 5–127; b) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; c) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; e) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007; f) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; g) J. Prunet, *Angew. Chem.* **2003**, *115*, 2932–2936; *Angew. Chem. Int. Ed.* **2003**, *42*, 2826–2830; h) R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4740–4782; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633; i) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238; j) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; k) K. C. Nicolaou, P. G. Bluger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4525; l) A. Gradillas, J. Pérez-Castells, *Angew. Chem.* **2006**, *118*, 6232–6247; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101.

[7] For previous examples of the use of RCM for construction of 12-membered aliphatic macrolides, see a) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803; b) A. Fürstner, T. Müller, *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821; c) S. Sasmal, A. Geyer, M. E. Maier, *J. Org. Chem.* **2002**, *67*, 6260–6263; d) M. D. Ronsheim, C. K. Zercher, *J. Org. Chem.* **2002**, *67*, 1878–1885; e) X. Wang, J. A. Porco, Jr., *Angew. Chem.* **2005**, *117*, 3127–3131; *Angew. Chem. Int. Ed.* **2005**, *44*, 3067–3071; f) M. Prakesch, U. Sharma, M. Sharma, S. Khadem, D. M. Leek, P. Arya, *J. Comb. Chem.* **2006**, *8*, 715–734.

[8] P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28.

[9] a) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235; b) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Org. Chem.* **1997**, *62*, 2328–2329.

[10] P. A. Grieco, Y. Masaki, D. Boxler, *J. Am. Chem. Soc.* **1975**, *97*, 1597–1599.

[11] S. Fukuzawa, H. Matsuzawa, S. Yoshimitsu, *J. Org. Chem.* **2000**, *65*, 1702–1706.

[12] The stereochemistries of the newly introduced hydroxy groups were checked by means of the modified Mosher's method.

[13] No other diastereomers were detected by ^{1}H NMR spectroscopy.

[14] I. Paterson, D. Wallac, C. J. Cowden, *Synthesis* **1998**, 639–652.

[15] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[16] For the metathesis catalysts we investigated, see a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956; c) R. R. Schrock, J. S. Murdzek, G. C. Bazan, M. Robbins, M. Dimare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886; d) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179; e) A. Michrowska, R. Bujok, R. S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, *J. Am. Chem. Soc.* **2004**, *126*, 9318–9325; f) H. Wakamatsu, S. Blechert, *Angew. Chem.* **2002**, *114*, 2509–2511; *Angew. Chem. Int. Ed.* **2002**, *41*, 2403–2405; g) N. Buschmann, H. Wakamatsu, S. Blechert, *Synlett* **2004**, 667–670.

[17] For the use of $Ti(OiPr)_4$ to prevent coordination of Ru to a carbonyl group, see a) A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136; b) A. K. Ghosh, J. Cappiello, D. Shin, *Tetrahedron Lett.* **1998**, *39*, 4651–4654.

[18] a) A. Fürstner, O. R. Thiel, L. Ackerman, H.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204–2207; b) S. H. Hong, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415.

[19] a) J. R. Gage, D. A. Evans, *Org. Synth.* **1989**, *68*, 83 – 91; b) P. C.-M. Chan, J. M. Chong, K. Kousha, *Tetrahedron* **1994**, *50*, 2703 – 2714; c) D. E. Cane, W. Tan, W. R. Ott, *J. Am. Chem. Soc.* **1993**, *115*, 527 – 535.
[20] Details are described in the Supporting Information.
[21] With -OTES: 55% yield, 86% *de*; with -OH: 64% yield, 94% *de*.
[22] See Figure S1 in the Supporting Information.
[23] For detailed experimental procedures and compound data, see the Supporting Information.
[24] Details of the chemical degradation of TES-protected pladienolide D are described in the Supporting Information.
[25] NOESY data are described in the Supporting Information (Figure S2).
[26] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370.
[27] H. Pine, R. Zahler, D. A. Evans, R. H. Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3270 – 3272.
[28] a) H. Nagano, E. Nakanishi, S. Takajo, M. Sakuma, K. Kudo, *Tetrahedron* **1999**, *55*, 2591 – 2608; b) J. D. White, J. P. Carter, H. S. Kezar III, *J. Org. Chem.* **1982**, *47*, 929 – 932.
[29] O. Mitsunobu, *Synthesis* **1981**, 1 – 28.
[30] H. S. Shultz, H. B. Freyermuth, S. R. Buc, *J. Org. Chem.* **1963**, *28*, 1140 – 1140.
[31] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976; b) Y. Gao, R. M. H. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780.
[32] L. A. Sarandeses, A. Mourino, J.-L. Luche, *J. Chem. Soc. Chem. Commun.* **1991**, 818 – 820.
[33] a) A. K. Chatterjee in *Handbook of Metathesis*, *Vol. 2* (Ed: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, pp. 246 – 295; b) A. K. Chatterjee, R. H. Grubbs, *Angew. Chem.* **2002**, *114*, 3303 – 3306; *Angew. Chem. Int. Ed.* **2002**, *41*, 3171 – 3174; c) F. D. Toste, A. K. Chatterjee, R. H. Grubbs, *Pure Appl. Chem.* **2002**, *74*, 7 – 10.
[34] T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 1123 – 1125.

