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Synthesis of the Macrocyclic Core of (−)-Pladienolide B

Philip R. Skaanderup*,†,‡ and Thomas Jensen†

Department of Chemistry, Technical University of Denmark, Building 201, Kemitorvet, DK-2800 Kgs. Lyngby, Denmark, and Novartis Institutes for BioMedical Research, Novartis AG, CH-4056 Basel, Switzerland

philip.skaanderup@novartis.com

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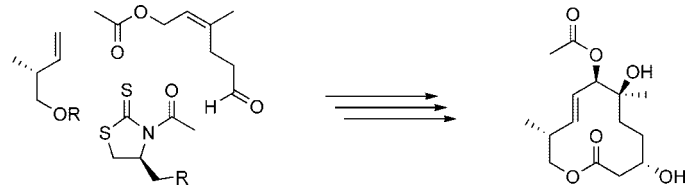
ABSTRACT



An efficient synthesis of the macrocyclic core of (−)-pladienolide B is disclosed. The concise route relies on a chiral auxiliary-mediated asymmetric aldol addition and an osmium-catalyzed asymmetric dihydroxylation to install the three oxygenated stereocenters of the macrocycle. This purely reagent-controlled and flexible strategy sets the stage for future analogue syntheses and structure−activity relationship plotting of the appealing anticancer lead structure pladienolide B.

The identification of new targets of clinical relevance is a cornerstone in improving the level of existing disease remedies and for developing new therapies for hitherto untreatable diseases.[1] Recently, it has been indicated that splicing factors are important potential targets for the development of new cancer therapies.[2] The natural product pladienolide B (**1**, Figure 1) potently inhibits cancer cell proliferation, and biological studies aimed at elucidating its mode of action have led to a proposed mechanism involving binding to the splicing factor SF3b.[3] Pladienolide B was isolated by Sakai and co-workers in 2004 from the fermentation broth of *Streptomyces platensis* Mer-11107 using a screen designed to identify compounds that inhibit cell signaling pathways in a tumor-specific microenvironment.[4a–c] Significantly, pladienolide B inhibts hypoxia-induced VEGF expression and proliferation of human cancer cell lines with low to subnanomolar IC_{50} values.[4a,c] Moreover, pladienolide B displays unchanged inhibitory activity against drug-resistant cancer cells, as compared to their parental cell lines, and has demonstrated complete regression of BSY-1 tumors in xenograft mice models.[4c] This unique biological profile has inspired considerable interest from the scientific community[5,6] leading to elucidation of the absolute stereochemistry[5] (**1**, Figure 1) and the first total synthesis by Kotake and co-workers.[6a,c] Despite these noteworthy efforts, little is known about the structural basis for pladienolide B's modulation of spliceosomal activity and potential interaction with other targets.

At the outset of our synthetic efforts in April 2005, only the planar structure of pladienolide B had been reported.[4b,7] Interestingly, the 12-membered core and the side chain of pladienolide B resemble the macrocyclic core of 10-

† Technical University of Denmark.
‡ Novartis Institutes for BioMedical Research.

(1) Fishman, M. C.; Porter, J. A. *Nature* **2005**, *437*, 491–493.
(2) (a) Karni, R.; de Stanchina, E.; Lowe, S. W.; Sinha, R.; Mu, D.; Krainer, A. R. *Nature Struc. Mol. Biol.* **2007**, *14*, 185–193. (b) He, X.; Pool, M.; Darcy, K. M.; Lim, S. B.; Auersperg, N.; Coon, J. S.; Beck, W. T. *Oncogene* **2007**, *26*, 4961–4968.
(3) Kotake, Y.; Sagane, K.; Owa, T.; Mimori-Kiyosue, Y.; Shimizu, H.; Uesugi, M.; Ishihama, Y.; Iwata, M.; Mizui, Y. *Nature Chem. Biol.* **2007**, *3*, 570–575.
(4) (a) Sakai, T.; Sameshima, T.; Matsufuji, M.; Kawamura, N.; Dobashi, K.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 173–179. (b) Sakai, T.; Asai, N.; Okuda, A.; Kawamura, N.; Mizui, Y. *J. Antibiot.* **2004**, *57*, 180–187. (c) Mizui, Y.; Sakai, T.; Iwata, M.; Uenaka, T.; Okamoto, K.; Shimizu, H.; Yamori, T.; Yoshimatsu, K.; Asada, M. *J. Antibiot.* **2004**, *57*, 188–196.
(5) Asai, N.; Kotake, Y.; Niijima, J.; Fukuda, Y.; Uehara, T.; Sakai, T. *J. Antibiot.* **2007**, *60*, 364–369.

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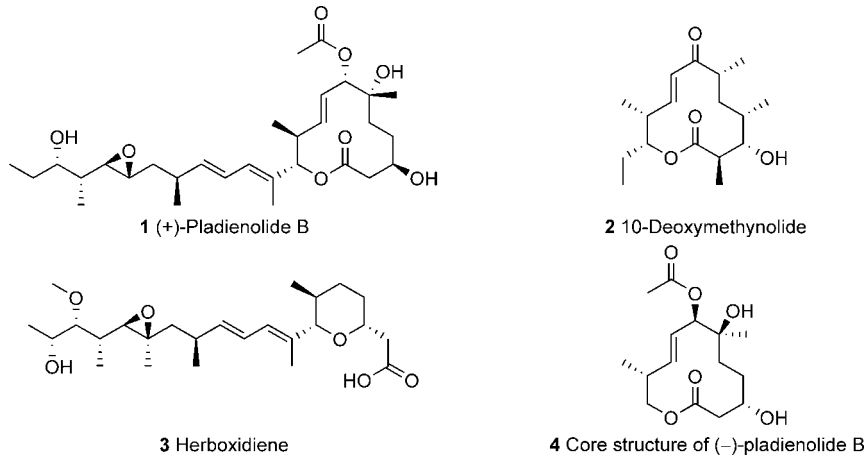
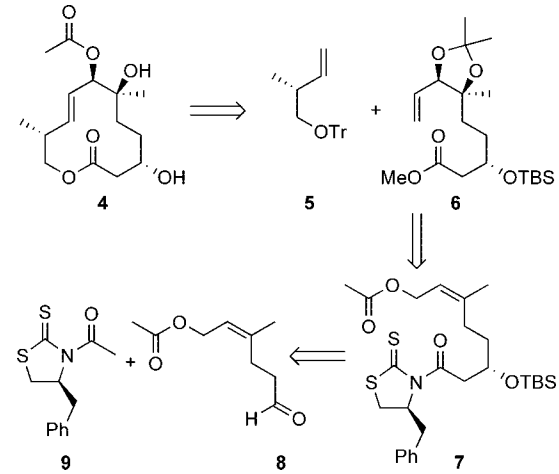


Figure 1. Metabolites of the *Streptomyces* family **1**−**3** and target structure **4**.

deoxymethynolide[8] (**2**, Figure 1) and the side chain of herboxidiene[9] (**3**). From an evolutionary point of view, it is conceivable that pladienolide B and other secondary metabolites produced by *Streptomyces* strains, such as herboxidiene and 10-deoxymethynolide, could be synthesized by polyketide synthases encoded by related gene clusters.[10] Consistent with a common biogenesis for these three polyketides, we projected that the absolute configuration of **1** would correlate to that of **2** and **3**. Hence, we focused our synthetic studies on the asymmetric synthesis of core structure **4**, the enantiomer of the (+)-pladienolide B core (Figure 1). Herein, we wish to report a convergent synthesis of **4** and its crystal structure.

Structurally, the core structure **4** consists of a 12-membered macrolactone bearing four stereocenters with an *O*-acetylated secondary alcohol adjacent to a tertiary hydroxyl group. The macrolactone also contains a disubstituted trans olefin, a tertiary stereocenter, and a second hydroxyl group stereocenter. Toward our synthetic target **4** we envisioned a strategy with maximum flexibility that would provide access to all sixteen stereoisomers of the core structure. Specifically, we envisioned an orthoester formation and ring-opening sequence to selectively acetylate the desired secondary alcohol and complete the synthesis of **4**. Macrolactonization and (*E*)-selective cross metathesis between olefins **5** and **6** could construct the 12-membered lactone. **5** would in turn be available from commercial (*S*)-Roche ester and **6** was anticipated to arrive from sequential olefination and osmium-catalyzed asymmetric dihydroxylation thereby installing the vicinal oxygen-substituted stereocenters of the macrocycle. Finally, key intermediate **7** would result from chiral auxiliary-mediated asymmetric aldol addition of known acetylthiazolidine-thione **9** and aldehyde **8** (Scheme 1).

Scheme 1. Retrosynthesis of (−)-Pladienolide B Core Structure



The synthesis takes advantage of the easily obtainable building blocks **5** and **8** (Scheme 2). Tritylation of (*S*)-Roche ester **10** followed by LAH reduction, Swern oxidation,[11] and Wittig methylenation afforded alkene **5** smoothly over this four-step sequence (Scheme 2a). Prilezhaev epoxidation[12] of commercial acetate **11** and subsequent epoxide cleavage

(6) (a) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350–4355. (b) Mandel, A. L.; Jones, B. D.; La Clair, J. J.; Burkart, M. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5159–5164. (c) Kanada, R. M.; Itoh, D.; Sakai, T.; Asai, N.; Kotake, Y.; Niijima, J. Eisai R & D Management Co., Ltd., Japan. PCT Int. Appl. WO 2007043621.

(7) The Danish Research Council for Technology and Production Sciences, grant no. 26-04-0143, Synthesis of Novel Pladienolide Analogues: Structure−Activity Relationship Mapping and Mode of Action Studies.

(8) Lambalot, R. H.; Cane, D. E. *J. Antibiot.* **1992**, *45*, 1981–1982.

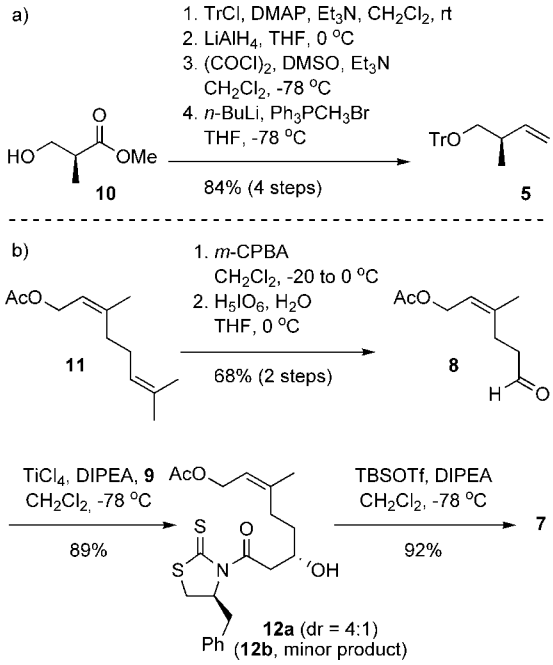
(9) Isaac, B. G.; Ayer, S. W.; Elliott, R. C.; Stonard, R. J. *J. Org. Chem.* **1992**, *57*, 7220–7226.

(10) (a) Zhao, L.; Ahlert, J.; Xue, Y.; Thorson, J. S.; Sherman, D. S.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 9881–9882. (b) Firn, R. D.; Jones, C. G. *Nat. Prod. Rep.* **2003**, *20*, 382–391. (c) Nguyen, T.; Ishida, K.; Jenke-Kodama, H.; Dittmann, E.; Gurgui, C.; Hocmuth, T.; Taudien, S.; Platzer, M.; Hertweck, C.; Piel, J. *Nat. Biotechnol.* **2008**, *26*, 225–233.

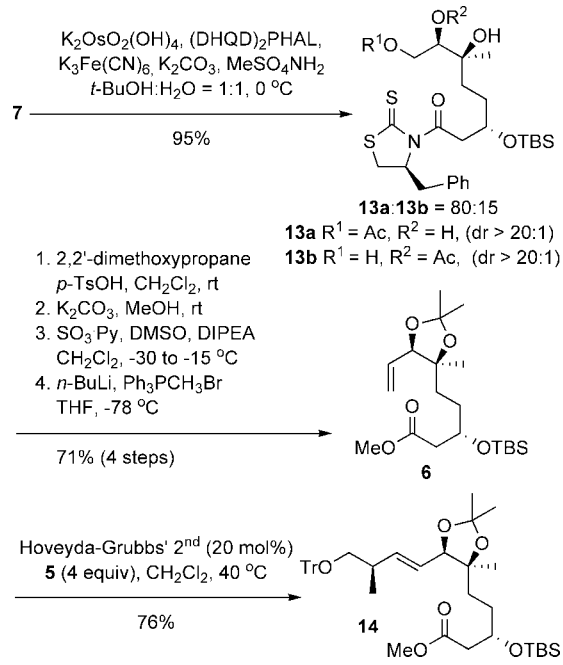
(11) (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3331. (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (c) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819–4822.

(12) Prilezhaev, N. *Ber.* **1909**, *42*, 4811–4815.

Scheme 2. Synthesis of Intermediates **5**, **8**, and **7**



Scheme 3. Synthesis of (*E*)-Olefin **14**



using periodic acid provided aldehyde **8**.[13] Secondary alcohol **12a** was available via an asymmetric aldol reaction of aldehyde **8** with a chiral acetylthiazolidinethione enolate generated from **9** using Vilarrasa's conditions.[14] The selectivity of the aldol reaction could be tuned to give either **12a** or **12b** as the major product even when the same acetylthiazolidinethione was employed. The titanium enolate generated with titanium tetrachloride and Hünig's base gave predominantly the desired isomer **12a** in excellent yield. If the enolate was generated from dichlorophenylborane and (−)-sparteine, **12b** was formed as the major product.[15] Additionally, the valine and *tert*-leucine-derived auxiliaries gave slightly improved product ratios of 5:1 to 6:1. However, we chose to use the phenylalanine-derived auxiliary because all intermediates leading to **9** are crystalline and can be obtained easily in analytically pure form. The aldol product was then protected as the TBS ether to give **7** in 92% yield (Scheme 2b).

The oxygenated functionality at the northern portion of the target molecule was installed by Sharpless's asymmetric dihydroxylation protocol.[16] From the well-defined olefin geometry of the substrate, which relates back to nerol and using the $(DHQD)_2PHAL$ ligand, diol **13a** was produced in good yield and selectivity greater than 20:1 at the newly formed stereocenters (Scheme 3). Acetate **13b** was also formed in equal diastereomeric ratio and is the likely product of intramolecular acetyl migration. All attempts to convert **13b** into **13a** were unsuccessful. The key alkene fragment **6** was prepared from **13a** in a four-step sequence initially involving acetonide formation and treatment with K_2CO_3 in methanol to concomitantly cleave the acetate and convert the chiral auxiliary into a methyl ester.[17] Parikh−Döering oxidation[18] followed by Wittig methylenation provided alkene **6** in 71% yield over these four steps. With compound **6** in hand, we set out to identify reaction conditions that would furnish (*E*)-alkene **14** efficiently. Initial attempts to mediate the cross-metathesis between olefins **5** and **6** with 10 mol% of either Grubbs' second-generation catalyst,[19] Hoveyda−Grubbs' second-generation catalyst,[20] or Grubbs' third-generation catalyst[21] gave the desired alkene **14** in less than 30% yield.[22] Interestingly, only the (*E*)-alkene was observed by ^1H NMR. Following optimization the yield of **14** could be improved to 76% using Hoveyda−Grubbs' second-generation catalyst and by adding **5** in two portions over the course of the reaction (Scheme 3). Selective deprotection of the trityl ether using a solution of BCl_3[23] followed by methyl ester hydrolysis successfully gave *seco*-acid **15** in 84% yield for this two-step sequence (Scheme 4).

(13) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269–5278.

(14) González, Á.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *49*, 8949–8952.

(15) Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23–25.

(16) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. For a recent review, see: (b) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, *11*, 1725–1756.

(17) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775–777.

(18) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

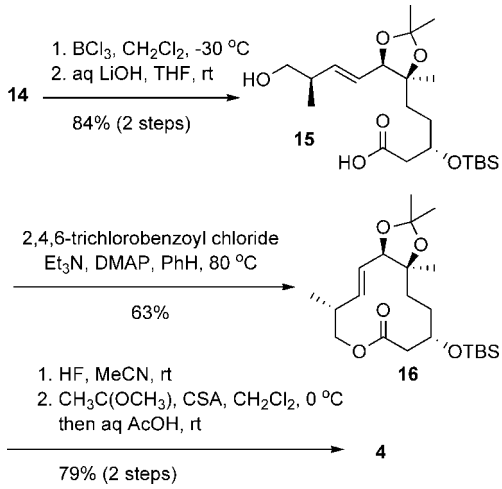
(19) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(20) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(21) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589–1592.

(22) Using the corresponding TBS-ether afforded the desired alkene in 25% yield; however, the TBS-ether was volatile and thus impractical to employ in the synthesis.

Scheme 4. Macrolactonization and Completion of **4**



Attempts to close the macrocycle under modified Yamaguchi conditions[24] at room temperature produced **16** in 34% yield. However, by increasing the reaction temperature to 80 °C and adding the preformed mixed anhydride slowly to a DMAP-benzene solution,[25] the yield improved considerably, and macrocycle **16** could be isolated in 63% yield. The TBS and acetonide groups were then effectively removed through the action of aqueous HF in MeCN.[26] Finally, the secondary allylic alcohol was acetylated selectively by treating the diol with trimethyl orthoacetate and CSA followed by cleavage of the resulting orthoester with aqueous AcOH to give the macrocyclic core structure **4** in 86% yield (Scheme 4).

The structure and absolute stereochemistry of macrolactone **4** were unambiguously established by single-crystal X-ray crystallography (Figure 2).[27]

In summary, the macrocyclic core of (−)-pladienolide B (**4**) has been synthesized in 8.1% overall yield starting from

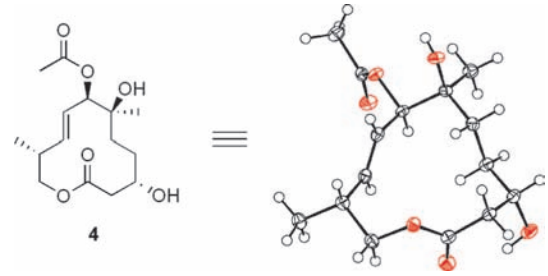


Figure 2. Structure of **4** in the crystal.[28] The ellipsoids are drawn at the 50% probability level, and the hydrogen atoms are drawn with an arbitrary radius. For the enantiomer shown, the Flack *x* parameter refined to 0.03(4).[29]

10 and **11** using a total number of 19 steps (longest linear = 15 steps). The achieved synthesis, with full control of all four stereocenters of the macrocyclic core structure, illustrates the flexibility of our approach. Through cross metathesis reactions between olefin **6** and homoallylic alcohols, as a readily available source of chemical diversity, our method sets the stage for rapid synthesis of new pladienolide analogues.[30] Our ongoing efforts are focused on using this strategy to synthesize new side-chain analogues and to study the structural basis for pladienolide B's anticancer activity.

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Supporting Information Available: Full experimental details and spectral data for all new compounds. This material is availabe free of charge via the Internet at http://pubs.acs.org.

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(23) Jones, G. B.; Hynd, G.; Wright, J. M.; Sharme, A. *J. Org. Chem.* **2000**, *65*, 263–265.
(24) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. For a recent review, see: (b) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939.
(25) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.
(26) Nicolaou, K. C.; Li, H.; Nold, A. L.; Pappo, D.; Lenzen, E. *J. Am. Chem. Soc.* **2007**, *129*, 10356–10357.
(27) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, deposition no. CCDC 682897.
(28) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7–13.
(29) (a) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881. (b) Parsons, S.; Flack, H. D. Abstracts of the 22nd European Crystallography Meeting, Budapest, 26−31 Aug 2004, Abstract No. MS22.
(30) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.