Natural Product Synthesis

Total Synthesis of the Antimitotic Marine Macrolide (−)-Leiodermatolide**

Ian Paterson,* Kenneth K.-H. Ng, Simon Williams, David C. Millican, and Stephen M. Dalby

Abstract: Leiodermatolide is an antimitotic macrolide isolated from the marine sponge Leiodermatium sp. whose potentially novel tubulin-targeting mechanism of action makes it an exciting lead for anticancer drug discovery. In pursuit of a sustainable supply, we report a highly stereocontrolled total synthesis (3.2% yield) based on a convergent sequence of palladium-mediated fragment assembly and macrolactonization. Boron-mediated aldol reactions were used to configure the three key fragments 2, 5, and 6 by employing the appropriate enantiomer of the lactate-derived ketone 7.

Tubulin-targeting compounds are perhaps the most validated subset of clinically important anticancer agents, with natural products and analogues representing the mainstay for current chemotherapy,[1–3] recently supplemented by the approval of the antibody–maytansinoid conjugate Kadcyla (trastuzumab emtansine).[2] Leiodermatolide (1; Scheme 1) was isolated (0.001% wet weight) by the Wright group in 2008 from the lithistid sponge Leiodermatium sp. collected by submersible off the Florida coastline.[4a] Leiodermatolide exhibits potent antiproliferative activity against a panel of human cancer cell lines (e.g. IC50 = 3.3 nM for A549 lung adenocarcinoma cells, 5.0 nM for PANC-1 pancreatic carcinoma cells), whilst showing reduced toxicity to normal cells. This activity appears to be mediated through the disruption of tubulin dynamics to induce cell-cycle arrest in the G2/M phase and apoptosis. Although the exact mechanism of action of leiodermatolide is currently unknown, it is clearly distinct from that of other tubulin-targeting drugs. Thus, leiodermatolide could serve as a promising lead compound for the development of new anticancer agents, provided a sustainable supply can be generated by chemical synthesis.[5–7]

From a structural perspective, leiodermatolide features a triply unsaturated 16-membered macrolactone appended at C9 with a carbamate group and at C15 with an E,E-dienyl side chain terminating in a δ-lactone ring. This unique structure incorporates a total of nine stereocenters. In association with the Wright research group,[4b] we elucidated the relative configuration of leiodermatolide by using a combination of homo- and heteronuclear NMR spectroscopic analysis, molecular modeling, and computational DP4 NMR prediction.[8] The resulting assignment for the C1–C16 region was further supported by our synthesis of a macrocyclic fragment with a truncated side chain,[5] whereas an alternative stereostructure could be ruled out on the basis of synthetic studies reported earlier.[6a] The full configuration of the isolated C1–C16 and C20–C25 stereocenters was only recently tied down.

Scheme 1. Retrosynthetic analysis and key fragments for the synthesis of leiodermatolide. Bz = benzoyl, PMB = para-methoxybenzyl, TBS = tert-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

From a structural perspective, leiodermatolide features a triply unsaturated 16-membered macrolactone appended at C9 with a carbamate group and at C15 with an E,E-dienyl side chain terminating in a δ-lactone ring. This unique structure incorporates a total of nine stereocenters. In association with the Wright research group,[4b] we elucidated the relative configuration of leiodermatolide by using a combination of homo- and heteronuclear NMR spectroscopic analysis, molecular modeling, and computational DP4 NMR prediction.[8] The resulting assignment for the C1–C16 region was further supported by our synthesis of a macrocyclic fragment with a truncated side chain,[5] whereas an alternative stereostructure could be ruled out on the basis of synthetic studies reported earlier.[6a] The full configuration of the isolated C1–C16 and C20–C25 stereocenters was only recently tied down.
with the first total synthesis of (−)-leiodermatolide (I) by the Fürstner research group employing an elegant strategy based on ring-closing alkene metathesis. [7] We now report a highly convergent total synthesis of (−)-leiodermatolide implementing a complementary macrolactonization strategy that also features the extensive application of our versatile lactate aldol chemistry [9] along with a variety of palladium-mediated coupling reactions. [10]

Building on the lessons learned from earlier synthetic efforts directed towards the macroyclic core, [5] Scheme 1 depicts the main retrosynthetic disconnections and key fragments 2–6 devised for the synthesis of leiodermatolide. The structure was initially simplified by disassembly of the 10Z,12Z-diene region and opening of the macrolactone ring in I to reveal the C1–C11 vinyl stannane 2 and the C12–C25 vinyl iodide 3 containing the entire side chain for a planned late-stage Stille coupling. The former fragment was then envisaged to be available by elaboration of vinyl triflate 4 through a Suzuki-type methylation and an anti-selective aldol reaction using (R)-7. The more elaborate fragment 3 would arise in turn through stereocontrolled installation of the 16E,18E diene by a Heck coupling between vinyl iodide 5 and the correctly configured allyl-substituted δ-lactone 6, constructed using (S)- and (R)-7, respectively.

The synthesis of vinyl stannane 2 utilized Roche ester derivative 8 as the source of the C6 methyl-bearing stereocenter (Scheme 2). [11] The required 4E-configured trisubstituted alkene was first introduced via the corresponding stereodefined vinyl triflate 4. In practice, controlled addition of TBSO(CH₂)₃MgBr to 8 provided the required ketone (88%), which was converted into 4 with high selectivity (82%, >20:1 Z/E) by treatment of the kinetically generated lithium enolate (LiHMDS) with the Comins reagent. [12] After screening various methods for methylation, Suzuki coupling of 4 with trimethylboroxine [13] (cat. [Pd(PPh₃)₄], K₂CO₃) was found to proceed well to afford the E alkene 9 (96%, >20:1 E/Z). Following cleavage of the PMB ether (DDQ) and Dess–Martin oxidation (69%), the resulting aldehyde 10 was treated with the E dicyclohexylboron enolate derived from (R)-7 (c-Hex₂BCl, Et₂N). [9] This matched aldol addition [14] afforded the anti adduct 11 (96%, d.r. >20:1) with a high level of control over the C7/C8 stereocenters.

Next, 11 was converted into ynone 12 (67%) by a sequence of silylation, (trimethylsilyl)acetylide addition, basic methanolation, and oxidative glycol cleavage. [15] The Z iodoenone could then be conveniently accessed through conjugate addition of NaI (AcOH, THF) [16] to 12 to afford 13 (8:1 Z/E, 81% yield of the isolated Z isomer). To set the C9 configuration, Evans–Saksena reduction [17] (Me₄NBH(OAc)₃, MeCN, AcOH) of 13 again and propanal to generate ketone 5 [18] (83%) by a third boron-mediated aldol reaction, this time between (S)- and (R)-7, respectively.

Reagents and conditions:

a) TBSO(CH₂)₃MgBr, THF, −78°C, 88%; b) LiHMDS, THF, Comins reagent, −78°C−20°C, 82%; c) (MeBO)₂, Pd(PPh₃)₄ (10 mol %), K₂CO₃, dioxane, 50°C, 96% (>20:1 E/Z); d) DDQ, pH 7 buffer, CH₂Cl₂, 84%; e) DMP, NaHCO₃, CH₂Cl₂, 82%; f) (R)-7, c-Hex₂BCl, Et₂N, EtO₂, −78°C−20°C, 96% (d.r. >20:1); g) TMSCl, imid, CH₂Cl₂, 96%; h) LiC(OTMS), THF, −78°C; i) K₂CO₃, MeOH; j) NaIO₂/SiO₂, CH₂Cl₂, 69% over 3 steps; k) NaI, AcOH, THF, 81% (8:1 Z/E); l) Me₂NBH(OAc)₂, MeCN, AcOH (3:1), −30°C, 97% (d.r. >20:1); m) Me₂C(O(Me)₂), PPTS, CH₂Cl₂, 99%; n) BuLi, Bu₂SnCl, Et₂O, −78°C, 88%; o) Na₂[μ-(μ-Cl)₂(μ-O)]₂, THF, −78°C, 97% (96% yield of the isolated Z isomer). The C9 stereocenter proceeded well to afford the 1,3-diene 14 (91% over 3 steps). Construction of the δ-lactone fragment 6 required the installation of three contiguous stereocenters, including the axial C21 allyl group. The C22/C23 configuration was set by a third boron-mediated aldol reaction, this time between (S)-7 and aldehyde 15 [18] to give the anti adduct 16 (90%, d.r. >20:1). Silylation (TBSOTf) of 16, selective reduction with LiAlH₄ (d.r. >20:1), and methanolation smoothly afforded diol 5 (91% over 3 steps). Construction of the δ-lactone fragment 6 required the installation of three contiguous stereocenters, including the axial C21 allyl group. The C22/C23 configuration was set by a third boron-mediated aldol reaction, this time between (S)-7 and aldehyde 15 [18] to give the anti adduct 16 (90%, d.r. >20:1). Silylation (TBSOTf) of 16, selective reduction with LiAlH₄ (d.r. >20:1), and methanolation smoothly afforded diol 5 (91% over 3 steps).
olefination of the aldehyde arising from oxidative glycol exclusively the required 16 oxidation at C1, and desilylation at C15 (TBAF) then selective desilylation at C1 and C21 (HF·py, pyridine), established the Z fragments.

Scheme 3. Preparation of vinyl iodide 3. Reagents and conditions: a) (S)-7, c-Hex-BCl, Et,N, Et,O, −78 → −20 °C, 90 % (d.r. > 20:1); b) TBSOTf, 2,6-lutidine, CH3Cl, −78 °C; c) LiAlH4, THF, −78 °C; d) K2CO3, MeOH, 91 % over 3 steps; e) c-Hex-BCl, Et,N, Et,O; EtCHO, −78 → −20 °C, 94 % (d.r. > 20:1); f) TBSOTf, 2,6-lutidine, CH3Cl, −78 °C, 98 %; g) H3C=CHCH2MgBr, THF, −78 °C; h) NaIO4, MeOH, pH 7 buffer, 85 % over 2 steps; i) 19, BF3·Et2O, CH3Cl, −78 °C; j) 3 M HCl, THF, H2O, 82 % over 2 steps (d.r. 10:1); k) TMSCl, imid, CH3Cl, 97 %; l) 5, Pd(OAc)2 (10 mol %), Ag2CO3, DMF, 80 °C, 73 %; m) NaIO4/SiO2, CH2Cl2; n) [ICH2PPh3]I, NaHMDS, THF, −78 °C → 80 °C = 98 %. Subsequent acid-mediated cyclization then provided δ-lactone 20 (82 %, 2 steps).[21] In this situation, 1,2-induction by Felkin–Anh control and 1,3-induction based on the Evans polar model are mutually reinforcing.[22] The NMR spectroscopic data for this synthetic material matched well with those for the corresponding 3-lactone.[23,29] But this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,30] a result anticipated from earlier studies with a truncated triol pointing 4:1 mixture of the C7 and C9 carbamates, [23,29] but this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates.[23,30] A sequence of hydroxy-group differentiation was sought to overturn the intrinsic substrate selectivity. Pleasingly, regiocontrolled silylation of leiodermatolide, and the stereochemical assignment secured, their controlled linkage to the full 25-carbon backbone of leiodermatolide was now executed (Scheme 4). Accordingly, Stille cross-coupling[26] of 2 and 3 under Fürstner conditions[26c] smoothly established the 10Z,12Z diene of 22 (80 %). A sequence of selective desilylation at C1 and C21 (HF·py, pyridine), oxidation at C1, and desilylation at C15 (TBAF) then provided the required seco acid 23 (51 % overall). Gratifyingly, Yamaguchi macro lactonization[23] served to efficiently close the 16-membered macro lactone. Acetonide cleavage then gave 24 (73 %), corresponding to the descarbamoyl derivative of leiodermatolide. Notably, the order of steps could be reversed, whereby acetonide cleavage was carried out first on 23 to give the unprotected tetraol, which was then macro lactonized to afford 24 with complete selectivity at C15.[23] Initially, we explored the introduction of the carbamate functionality on triol 24 itself by treatment with Cl3CCONCO (CH3Cl, −78 °C).[24] But this reaction only afforded a disappointing 41 % mixture of the C7 and C9 carbamates,[23,29] a result anticipated from earlier studies with a truncated macro lactone core.[23] To solve this problem, an effective sequence of hydroxy-group differentiation was sought to overturn the intrinsic substrate selectivity. Pleasingly, regiocontrolled silylation at C7 (1-(trimethylsilyl)imidazole; PPTS, MeOH) gave the corresponding C9/C21 diol, the treatment of which with Cl3CCONCO and acidic workup exclusively afforded (−)-leiodermatolide (1, 53 %; \( \delta_{\text{H}}^{1} = -74.0 \) (c = 0.027, MeOH); lit.[28] \( \delta_{\text{H}}^{1} = -84.2 \) (c = 0.34, MeOH)). To our satisfaction, all \( \text{H} \) and \( \text{C} \) NMR spectroscopic data for this synthetic material.

Scheme 4. Completion of leiodermatolide (1). Reagents and conditions: a) [Pd(PPh3)4] (10 mol %), CuTC, Bu4NPF6, POCl3, DMF, 80 %; b) HF·py, pyridine, THF; c) TEMPO, PhIOAc, CH3Cl; d) NaClO4, NaOH, POCl3, 2-methyl-2-butene, BuOH, H2O, THF; e) TBAF, THF, 50 °C, 51 % over 4 steps; f) TBCC, Et,N, THF; DMAP, PhMe, 80 %; g) Dowex 50WX8, MeOH, 91 %; h) TMS-imidazole, CH3Cl, PPTS, MeOH; Cl3CCONCO, CH3Cl, −78 °C; Al2O3; PPTS, MeOH, 53 %. DMAP = 4-dimethylaminopyridine, py = pyridine, TBAF = tetrabutylammonium fluoride, TC = 2-thiophenecarboxylate, TCBC = 2,4,6-trichlorobenzoyl chloride, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl.
correlated with those recorded for an authentic sample of natural leiodermatolide.

In conclusion, we have achieved a highly convergent total synthesis of the antimitotic marine macrolide (−)-leiodermatolide (1) in 23 steps and 3.2% yield. This route features a uniformly high level of stereocontrol relying on lactate aldol chemistry,[9] combined with expedient fragment assembly based on a variety of palladium-catalyzed coupling reactions and an efficient macrolactonization step. It should be amenable to the synthesis of useful quantities of this otherwise scarce yet highly promising anticancer agent[30] for further biological evaluation and should also enable structure–activity-relationship studies. Indeed, we have already prepared the first novel leiodermatolide analogues in the form of triol 24 and the regioisomeric C7 carbamate.[31]

Received: November 22, 2013
Published online: January 30, 2014

Keywords: aldol reaction · antitumor agents · cross-coupling · macrolides · total synthesis

[1] a) K. H. Alltman, J. Gertsch, Nat. Prod. Rep. 2007, 24, 327; b) G. M. L. Cragg, D. G. I. Kingston, D. J. Newman, Anticancer Agents from Natural Products, Taylor & Francis Group, Boca Raton, 2005; c) M. Kavallaris, N. M. Verrills, B. T. Hill, Drug Resist. Updates 2001, 4, 392.
[2] S. Verma, D. Miles, L. Gianni, I. E. Krop, M. Welslau, J. Baselage, M. Pegram, D.-Y. Oh, V. Diéras, E. Guardino, L. Fang, M. W. Lu, S. Olsen, K. Blackwell, N. Engl. J. Med. 2012, 367, 1783.
[3] Correction: S. Verma, D. Miles, L. Gianni, I. E. Krop, M. Welslau, J. Baselage, M. Pegram, D.-Y. Oh, V. Diéras, E. Guardino, L. Fang, M. W. Lu, S. Olsen, K. Blackwell, N. Engl. J. Med. 2013, 368, 2442.
[4] a) G. M. Cragg, D. J. Newman, Biochim. Biophys. Acta Gen. Subj. 2013, 1830, 3670; b) S. M. Dalby, I. Paterson, Curr. Opin. Drug Discov. Devel. 2010, 13, 777; c) G. M. Cragg, P. G. Grothaus, D. J. Newman, Chem. Rev. 2009, 109, 3012; d) I. Paterson, E. A. Anderson, Science 2005, 310, 451; e) I. Paterson, K.-S. Yeung, Chem. Rev. 2005, 105, 4257.
[5] a) A. E. Wright, J. K. Reed, J. Roberts, R. E. Longley, U.S. Pat. Appl. Publ. (USA), US2008013050, 14 pp. [Chem. Abstr. 2008, 149, 230103]; b) I. Paterson, S. M. Dalby, J. C. Roberts, G. J. Naylor, E. A. Guzmán, R. Isbrucker, T. P. Pitts, P. Linley, D. Divilianska, J. K. Reed, A. E. Wright, Angew. Chem. 2011, 123, 3277; Angew. Chem. Int. Ed. 2011, 50, 32196.
[6] a) G. R. C. Rink, V. Navickas, M. E. Maier, Org. Lett. 2011, 13, 4398.
[7] a) C. Rink, V. Navickas, M. E. Maier, Org. Lett. 2011, 13, 2334; b) V. Navickas, C. Rink, M. E. Maier, Synlett 2011, 191.
[8] b) J. Willwacher, N. Kausch-Busies, A. Fürstner, Angew. Chem. 2012, 124, 12207; Angew. Chem. Int. Ed. 2012, 51, 12041.
[9] S. G. Smith, J. M. Goodman, J. Am. Chem. Soc. 2010, 132, 12946.
[10] a) I. Paterson, D. J. Wallace, S. M. Velázquez, Tetrahedron Lett. 1994, 35, 9083; b) I. Paterson, D. J. Wallace, Tetrahedron Lett. 1994, 35, 9087; c) I. Paterson, D. J. Wallace, C. J. Cowden, Synthesis 1998, 639.
[11] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, Angew. Chem. 2005, 117, 4516; Angew. Chem. Int. Ed. 2005, 44, 4442.
[12] a) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, J. Am. Chem. Soc. 2001, 123, 9535; b) I. Paterson, E. A. Arnott, Tetrahedron Lett. 1998, 39, 7185.
[13] a) T. Mukaiyama, K. Banno, K. Narasaka, J. Am. Chem. Soc. 1994, 96, 7593; b) J. D. White, R. Plakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Kcown, C. S. Nylund Kolz, B. W. Phillips, J. Org. Chem. 2002, 67, 7750.
[14] S. Crossman, M. V. Perkins, J. Org. Chem. 2006, 71, 117.
[15] a) T. Makiyama, K. Banno, K. Narasaka, J. Am. Chem. Soc. 2012, 134, 12467; Angew. Chem. Int. Ed. 2013, 52, 9007.
[16] Intermediate 20 also featured in the synthesis by the Fürstner group (Ref. [7]), although it was prepared by an entirely different route. They converted this compound into a vinyl boronate by olefin metathesis and then employed a Suzuki cross-coupling to construct the C17–C18 bond.
[17] a) D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Young, J. Am. Chem. Soc. 1996, 118, 4322.
[18] See the Supporting Information for full details.
[19] T. Jeffery, J. Soc. Chem. Commun. 1991, 324.
[20] G. Stork, K. Zhao, Tetrahedron Lett. 1989, 30, 2173.
[21] a) A. Fürstner, J. A. Funel, M. Tremblay, L. B. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, Chem. Commun. 2008, 2873; b) J. K. Stille, B. L. Groh, J. Am. Chem. Soc. 1987, 109, 813.
[22] J. Inanaga, K. Hira, H. Saeki, T. Katsuki, M. Yamaguchi, Bull. Chem. Soc. Jpn. 1979, 52, 1899.
[23] a) P. Kočovský, Tetrahedron Lett. 1986, 27, 5521; b) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, Angew. Chem. 2000, 112, 385; Angew. Chem. Int. Ed. 2000, 39, 377.
[24] This reaction was also accomplished by formation of the biscarbamate. In contrast, silylation of 24 with chlorotriethylsilane occurred exclusively at the sterically more accessible C9 allylic alcohol. We attribute the contrasting carbamoylation results with the 1,3-diol 24 to a more complex cyclic mechanism; see: G. Raspoet, M. T. Nguyen, M. McGarraghy, A. F. Hegarty, J. Org. Chem. 1998, 63, 6878.
[25] For leading references to syntheses of other anticancer macrolides by our research group, see: a) S. M. Dalby, J. Goodwin-Tindall, I. Paterson, Angew. Chem. 2013, 125, 6645; Angew. Chem. Int. Ed. 2013, 52, 6517; b) I. Paterson, S. J. Fink, L. W. Lee, S. J. Atkinson, S. B. Blakey, Org. Lett. 2013, 15, 3118; c) I. Paterson, P. Maltus, S. M. Dalby, J. H. Lim, E. A. Anderson, Angew. Chem. 2012, 124, 2803; Angew. Chem. Int. Ed. 2012, 51, 2749; d) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, H. Knust, J. Stafford, Chem. Asian J. 2008, 3, 367; e) I. Paterson, R. Britton, O. Delgado, N. M. Gardner, A. Meyer, G. J. Naylor, K. G. Poullennec, Tetrahedron 2010, 66, 6534; f) I. Paterson, T. Paquet, Org. Lett. 2010, 12, 2158.
[26] Detailed biological studies will be reported elsewhere.