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Total Synthesis of TAK-Kinase Inhibitor LL-Z1640-2 via Consecutive Macrocyclization and Transannular Aromatization†

Hideki Miyatake-Ondozabal and Anthony G. M. Barrett*

Department of Chemistry, Imperial College, London SW7 2AZ, England

agm.barrett@imperial.ac.uk

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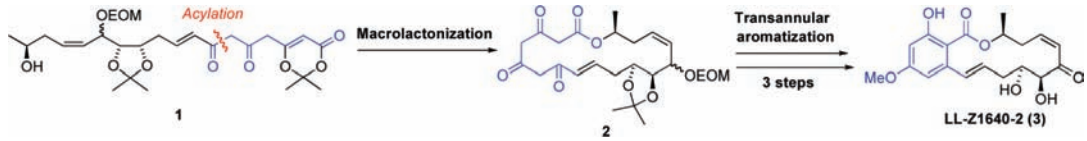
ABSTRACT



The biomimetic total synthesis of LL-Z1640-2 (3) is reported without the use of phenol protection. The aromatic unit was constructed via the transannular aromatization of macrocyclic triketo-ester 2, which in turn was synthesized by macrolactonization using an intramolecular trapping of a triketo-ketene derived from dioxinone 1.

The macrocyclic nonaketide, LL-Z1640-2 (**3**) (Figure 1), was first isolated as an antiprotozoan from an unidentified fungi by Ellestad et al.[1] in 1978 and belongs to a family of resorcylic acid lactones (RALs). Due to its unique chemical structure, particularly the *cis*-enone moiety, it is known as a potent irreversible, yet selective, inhibitor of transforming growth factor (TGF)-β-activated kinase 1 (TAK1, $IC_{50} = 8.1$ nM).[2,3] These types of *cis*-enone RALs have also been shown to inhibit mammalian cell proliferation and tumor growth in animals.[4] As a result of its useful biological activities and chemical structure, several total syntheses have been reported since its isolation.[2,5]

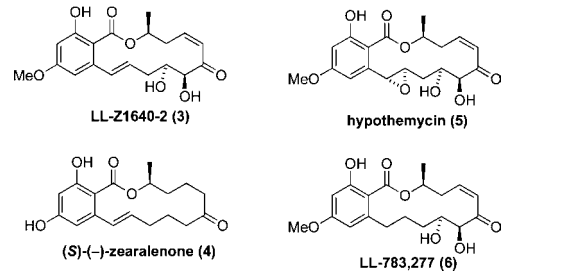


Figure 1. Structure of LL-Z1640-2 (**3**) and related resorcylate lactones.

In all the previous syntheses, the 14-membered macrocycle was constructed by an intramolecular Suzuki coupling reaction,[5b,d] Mukaiyama cyclization,[5a,c,d] or Mitsunobu macrolactonization,[2,5c−e] where the phenol groups were protected throughout the synthesis. An alternative strategy was also described by Henry et al., which relied on ring-closing metathesis (RCM) to generate the 14-membered ring.[6]

† This paper is dedicated to Professor Siegfried Blechert on the occasion of his 65th birthday in March 2011.

(1) Ellestad, F.; Lovell, M. F.; Perkinson, A. N.; Hargreaves, T. R.; McGahren, J. W. *J. Org. Chem.* **1978**, *43*, 2339.

(2) Schirmer, A.; Kennedy, J.; Murli, S.; Reid, R.; Santi, V. D. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 4234.

(3) Dakas, P. Y.; Barluenga, S.; Totzke, F.; Zirrgiebel, U.; Winssinger, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 6899.

(4) (a) Camacho, R.; Staruch, M. J.; DaSilva, C.; Koprak, S.; Sewell, T.; Salituro, G.; Dumont, F. J. *Immunopharmacology* **1999**, *44*, 255. (b) Tanaka, H.; Nishida, K.; Sugita, K.; Yoshida, T. *Jpn. J. Cancer Res.* **1999**, *90*, 1139. (c) Williams, D. H.; Wilkinson, S. E.; Purton, T.; Lamont, A.; Flotow, H.; Murray, E. J. *Biochemistry* **1998**, *37*, 9579.

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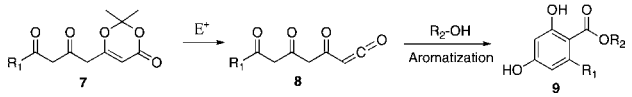
Recently, we reported the novel biomimetic syntheses of bioactive resorcylate natural products **9** utilizing an intermolecular ketene trapping and late-stage aromatization[7] approach starting from diketo-dioxinone **7** (Scheme 1).[8,9]

Scheme 1. Use of Diketo-dioxinones **7** as Precursors for the Synthesis of Resorcylates **9**

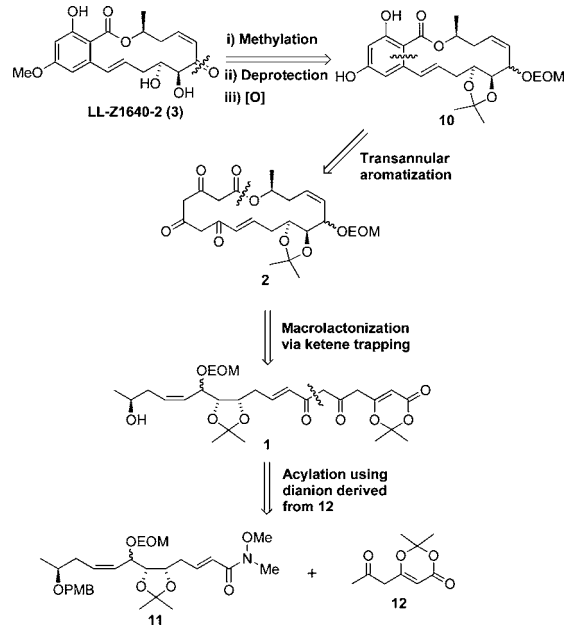


This methodology was recently extended to intramolecular ketene trapping and transannular aromatization, replacing the use of RCM for macrolactonization. The efficacy of this novel strategy was first demonstrated through the application for the synthesis of the resorcylic acid lactone, (*S*)-(−)-zearalenone (**4**).[10] This ketene trapping macrocyclization process is an adaption of the excellent methodology introduced by Boeckman and applied by others.[11]

Herein, we report a novel and efficient biomimetic synthesis of LL-Z1640-2 (**3**), without phenol protection, where macrolactonization and transannular aromatization are carried out consecutively to build the resorcylic core. It is noteworthy that this intramolecular ketene trapping-late-stage aromatization approach should be sufficiently concise for analogue synthesis such as mitogen-activated protein kinase (MAPK) inhibitor hypothemycin (**5**) and MAPK kinase (MEK) inhibitor LL-783,277 (**6**).

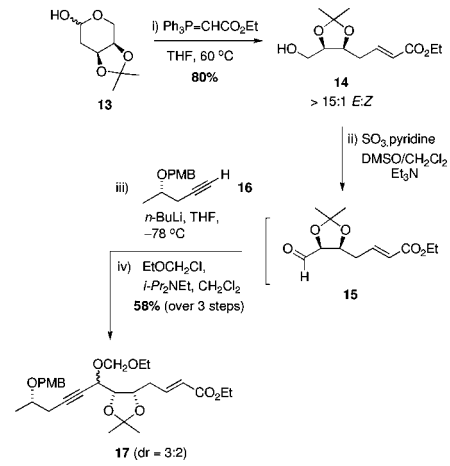
Our retrosynthetic analysis is illustrated in Scheme 2. LL-Z1640-2 (**3**) should be available following methylation, acetonide and EOM deprotection, and selective allylic oxidation of resorcylate **10**. We considered that the resorcylate unit could be constructed by late-stage transannular aromatization of macrocyclic triketo-ester **2**, which may be prepared by macrolactonization via intramolecular trapping of the ketene derived from diketo-dioxinone **1**. This in turn could be synthesized by acylation of Weinreb amide **11** with the dianion derived from keto-dioxinone **12**.

Scheme 2. Retrosynthetic Analysis of LL-Z1640-2 (**3**)



Weinreb amide **11** was synthesized in seven steps from commercially available 2-deoxy-D-ribose (Schemes 3 and 4).

Scheme 3. Synthesis of Dioxolane **17**



Lactol **13**[12] was subjected to Wittig olefination to give α,β-unsaturated ester **14** (80%) with excellent *E*:*Z* selectivity. Following Parikh−Doering oxidation, aldehyde **15** was obtained, and subsequent treatment with the lithiated alkyne

(5) (a) Tatsuta, K.; Takano, S.; Sato, T.; Nakano, S. *Chem. Lett.* **2001**, 172. (b) Sellès, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4627. (c) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, 22. (d) Hofmann, T.; Altmann, H.-K. *C. R. Chim.* **2008**, *11*, 1318. (e) Dakas, P. Y.; Jogireddy, R.; Valot, G.; Barluenga, S.; Winssinger, N. *Chem.—Eur. J.* **2009**, *15*, 11490.

(6) Henry, N.; Murray, M. N.; Robertson, N.; Marquez, R. *Tetrahedron Lett.* **2007**, *48*, 6088.

(7) (a) Harris, C. M.; Harris, T. M. *Tetrahedron* **1977**, *33*, 2159. (b) Hubbard, J. S.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2566.

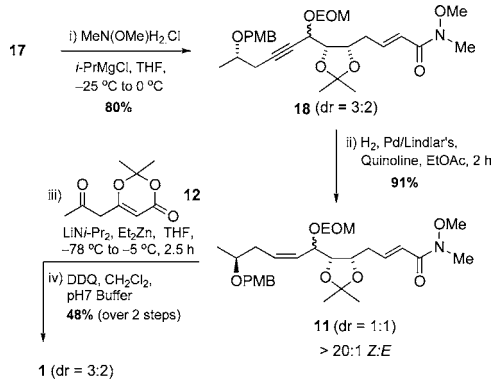
(8) (a) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293. (b) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910. (c) Basset, J.-F.; Leslie, C.; Hamprecht, D.; White, A. J. P.; Barett, A. G. M. *Tetrahedron Lett.* **2010**, *51*, 783. (d) Navarro, I.; Pöverlein, C.; Schlingmann, G.; Barrett, A. G. M. *J. Org. Chem.* **2009**, *74*, 8139.

(9) The diketo-dioxinones and triketo-compounds exist as keto-enol mixture. For simplicity, keto-forms are drawn.

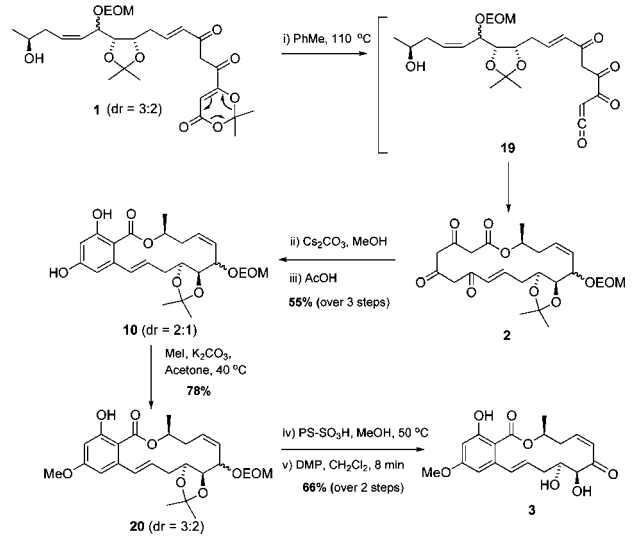
(10) Miyatake-Ondozabal, H.; Barrett, A. G. M. *Tetrahedron* **2010**, *66*, 6331.

(11) Boeckman, R. K. Jr.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. Boeckman, R. K., Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572. Boeckman, R. K., Jr.; Goldstein, S. W. *Total Synth. Nat. Prod.* **1988**, *7*, 1. Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486. Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P. E. *J. Am. Chem. Soc.* **1986**, *108*, 5549. For application of intramolecular capture of acyl-ketenes in natural product synthesis, see the excellent review by: Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022.

Scheme 4. Synthesis of Weinreb Amide **11** and Diketo-dioxinone **1**



Scheme 5. Synthesis of LL-Z1640-2 (**1**)



16[13] followed by ethoxymethylation of the resulting propargylic alcohol gave alkyne **17** in 58% yield over three steps. The corresponding Weinreb amide **18** was obtained via nucleophilic substitution at −25 °C in 80% yield (Scheme 4). Lindlar reduction of alkyne **18** provided exclusively the *Z*-alkene **11** (91%). Alkylation of Weinreb amide **11** with the enolate dianion[8b,d] derived from keto-dioxinone **12**,[8b] followed by *p*-methoxybenzyl deprotection, provided the key hydroxy-ketene precursor **1** in 48% yield over two steps. Transmetalation of dilithium enolate using diethylzinc was essential for minimizing the formation of the Michael addition adduct and also to achieve complete consumption of Weinreb amide **11**.

Thermolysis of diketo-dioxinone **1** resulted in generation of ketene **19**[14] which was efficiently trapped intramolecularly by the alcohol to provide the 18-membered macrocyclic lactone **2** (Scheme 5).[10] Subsequent transannular aromatization, using cesium carbonate, and acidification gave the desired resorcylate **10** in 55% yield. Regioselective methylation was achieved utilizing methyl iodide in acetone to give ether **20** (78%). Treatment with polymer-supported sulfonic acid in methanol resulted in full deprotection,[5d,e] and allylic oxidation using Dess−Martin periodinane[5a,c] gave LL-Z1640-2 (**3**) in 66% yield over two steps. The synthetic LL-Z1640-2 (**3**) displayed physical and spectroscopic data identical to an authentic sample.[15]

In summary, we report a 15-step biomimetic total synthesis of the TAK-kinase inhibitor LL-Z1640-2 (**3**) from commercially available starting materials. The key steps involved the use of intramolecular ketene trapping and transannular aromatization in a one-pot procedure to build the resorcylic core in high yields.

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Supporting Information Available: Experimental procedures for the synthesis of all new compounds, along with characterization data and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1983**, *116*, 312.

(13) White, J. D.; Somers, T. C.; Nagabushana Reddy, G. *J. Org. Chem.* **1992**, *57*, 4991. Kobayashi, Y.; Yoshida, S.; Asano, M.; Takeuchi, A.; Acharya, H. P. *J. Org. Chem.* **2007**, *72*, 1707. Paquette, L. A.; Hofferberth, J. E. *J. Org. Chem.* **2003**, *68*, 2266.

(14) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

(15) Commercially available from Aldrich Chemical Co.