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A chemoenzymatic and enantioselective total synthesis of the resorcylic acid lactone L-783,290, the *trans*-isomer of L-783,277

Andrew Lin, Anthony C. Willis, Martin G. Banwell *

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

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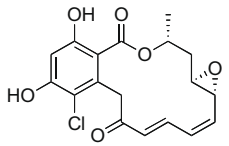
ABSTRACT

The structure, **5**, assigned to the resorcylic acid lactone L-783,290 has been prepared for the first time and in a modular fashion using a Heck reaction to link the readily available fragments **8** and **14**. Chemoenzymatic methods were used to prepare the latter fragment, in enantiopure form, from chlorobenzene.

The mycotoxins known as resorcylic acid lactones (RALs) constitute a significant group of 14-membered and benzannulated macrolides that have been isolated from a wide range of microfungi.[1] Representative examples of these types of natural products include radicicol (**1**, a HSP-90 inhibitor),[2] zearalenone (**2**, an oestrogen agonist),[3] hypothemycin (**3**, a MAP kinase inhibitor)[4] and L-783,277 (**4**, a MEK inhibitor).[5] The remarkable range of potent biological properties displayed by such compounds has attracted a great deal of attention.[1] Indeed, a number of RALs are considered important leads for the development of new therapeutic agents for the treatment of a range of human disease states, particularly cancer.[1] This situation has resulted in extensive efforts to develop economical and flexible routes to the RALs[1,6] and various analogues.[7]



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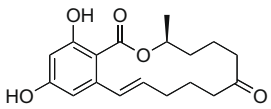

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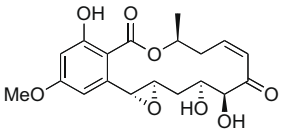

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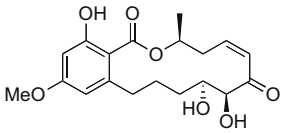

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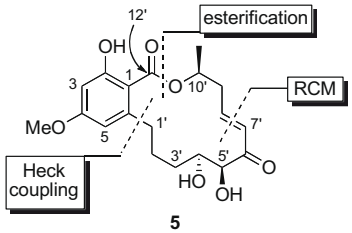
Herein we describe the first synthesis of the structure, **5**, assigned to L-783,290,[5b] the *trans*-isomer and co-metabolite of the RAL L-783,277 (**4**).[5,8] Both compounds were isolated from a *Phoma spp.* (ATCC 74403) by bioassay-guided fractionation using a kinase screen.[5] L-783,277 is a potent and irreversible inhibitor of MEK, a threonine/tyrosine-specific MAP kinase (IC_{50} of 4 nM) and a slightly weaker inhibitor of Lck kinase (IC_{50} 750 nM). L-783,290 showed an IC_{50} of 300 nM when tested as an inhibitor of MEK.



5

Our synthesis is a modular one that combines three fragments corresponding to C1–C6 + C12′, C1′–C6′ and C8′–O11′ of target **5**. The key bond-forming events are shown in structure **5** and involve, in order of execution, Heck coupling, esterification and ring-closing metathesis (RCM) processes. In contrast to the other processes, the Heck reaction is rarely applied in the synthesis of RALs[1a,9] despite the potential it offers for introducing relevant functionality found in the C1′–C3′ region of many of the more biologically active members of this class of natural product.

The synthesis of the aromatic fragment corresponding to C1–C6 + C12′ of target **5** was straightforward (Scheme 1). Thus,

* Corresponding author. Tel.: +61 2 6125 8202; fax: +61 2 6125 8114.
E-mail address: mgb@rsc.anu.edu.au (M.G. Banwell).

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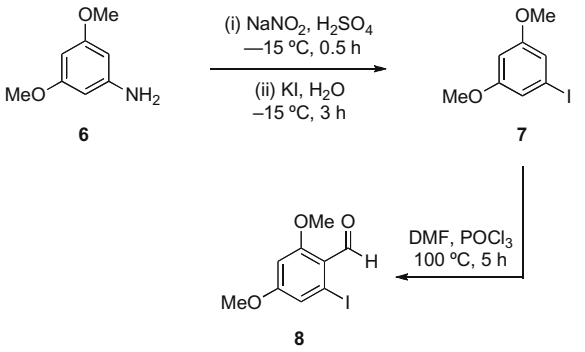
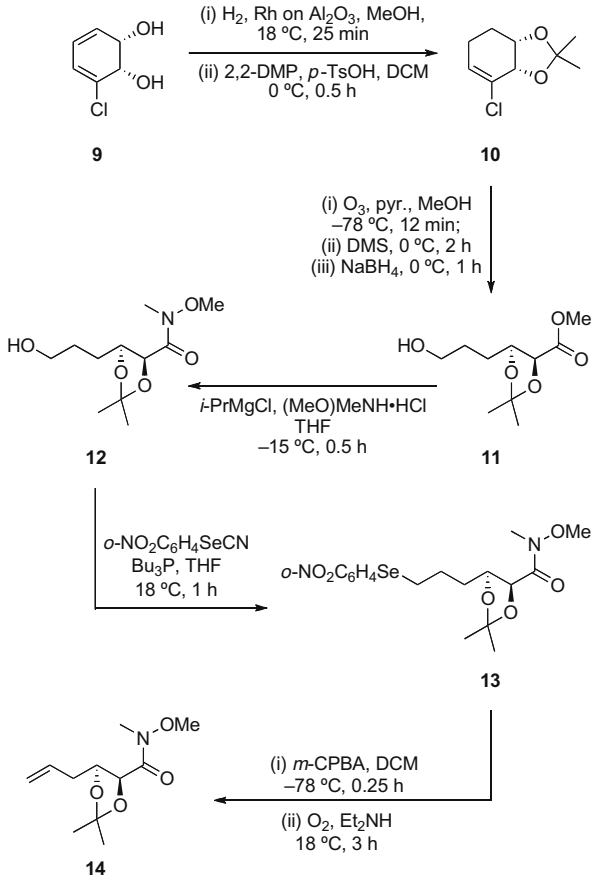


Scheme 1.

subjection of the commercially available dimethoxyaniline **6** to a Sandmeyer reaction using potassium iodide as the nucleophilic source gave aryl iodide **7** in 71% yield. Reaction of the latter compound with DMF/$POCl_3$ under Vilsmeier–Haack conditions then afforded, as a crystalline solid, the required and previously reported[10] benzaldehyde **8** (63%).

A chemoenzymatic pathway was employed in the enantioselective assembly of the C1′–C6′ fragment. As shown in Scheme 2, the reaction sequence starts with the enantiomerically pure and commercially available *cis*-1,2-dihydrocatechol **9** derived from the whole-cell biotransformation of chlorobenzene.[11] The non-chlorinated double bond in this diene can be selectively hydrogenated in the presence of rhodium on alumina and the resulting chlorocyclohexene[12,13] readily converted, under conventional conditions involving the use of 2,2-dimethoxypropane (2,2-DMP) and *p*-TsOH in dichloromethane, into the acetonide **10**[13] (63%). Subjection of a methanolic solution of compound **10** to ozonolysis at −78 °C followed by treatment of the intermediate ozonide with dimethyl sulfide and in situ reduction of the ensuing aldehyde with sodium borohydride gave the hydroxy ester **11** in 76% yield. This was readily converted, under conditions defined by Williams et al.,[14] into the Weinreb amide **12** (90%) which was itself converted into the corresponding *o*-nitrophenylselenide **13** (89%) using conditions reported by Grieco et al.[15] Finally, treatment of compound **13** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 and exposure of the resulting selenoxides to diethylamine and oxygen then gave the olefin **14** (93%) required for the subsequent Heck reaction. The structure of this pivotal building block was confirmed by a single-crystal X-ray analysis.[16]



Scheme 2.

Extensive experimentation was required to achieve an operationally useful Heck coupling of aryl iodide **8** and terminal alkene **14** (Scheme 3). Under the best conditions identified thus far,[17] heating a DMF solution of a 1:1.5 molar mixture of the substrates in the presence of $Pd(OAc)_2$, potassium carbonate and tetra-*n*-butylammonium bromide (TBAB) at 80 °C for 40 h provided a ca. 8:1 mixture of coupling product **15** and its *Z*-isomer in 56% combined yield at 80–90% conversion. Pinnick-type oxidation[18] of the chromatographically purified aldehyde **15** gave acid **16** in 75% yield and the latter compound was hydrogenated in the presence of 10% palladium on carbon to give the corresponding saturated system **17** (97%). Subjection of acid **17** to Mitsunobu esterification[19] with the commercially available and enantiomerically pure unsaturated alcohol **18** gave the ester/amide **19** (90%) that was treated with vinyl magnesium bromide and so affording the diene **20** required for the pivotal RCM reaction. When a 1.5 mM solution of compound **20** in CH_2Cl_2 was treated with Grubbs' second-generation catalyst[20] the smooth production of macrolide **21** was observed and this was obtained in 48% overall yield from precursor **19**. In the final step of the reaction sequence, compound **21** was treated with BCl_3 in CH_2Cl_2 at −78 °C[6h] and then subjected to aqueous work-up. This sequence resulted in simultaneous cleavage of the C-2 *O*-methyl ether and hydrolysis of the acetonide unit thus affording the target macrolide **1** in 60% yield and as a white, crystalline solid.

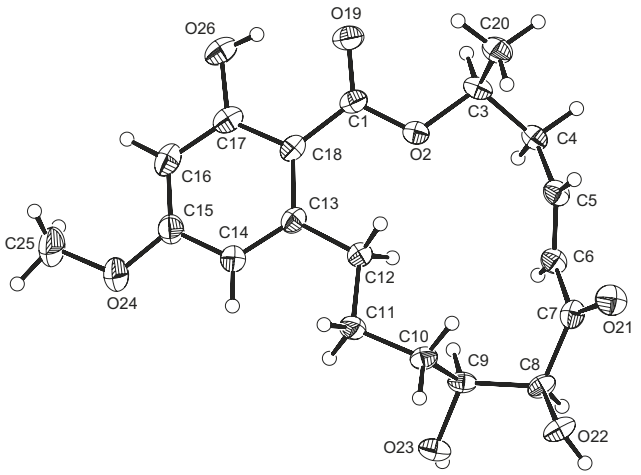
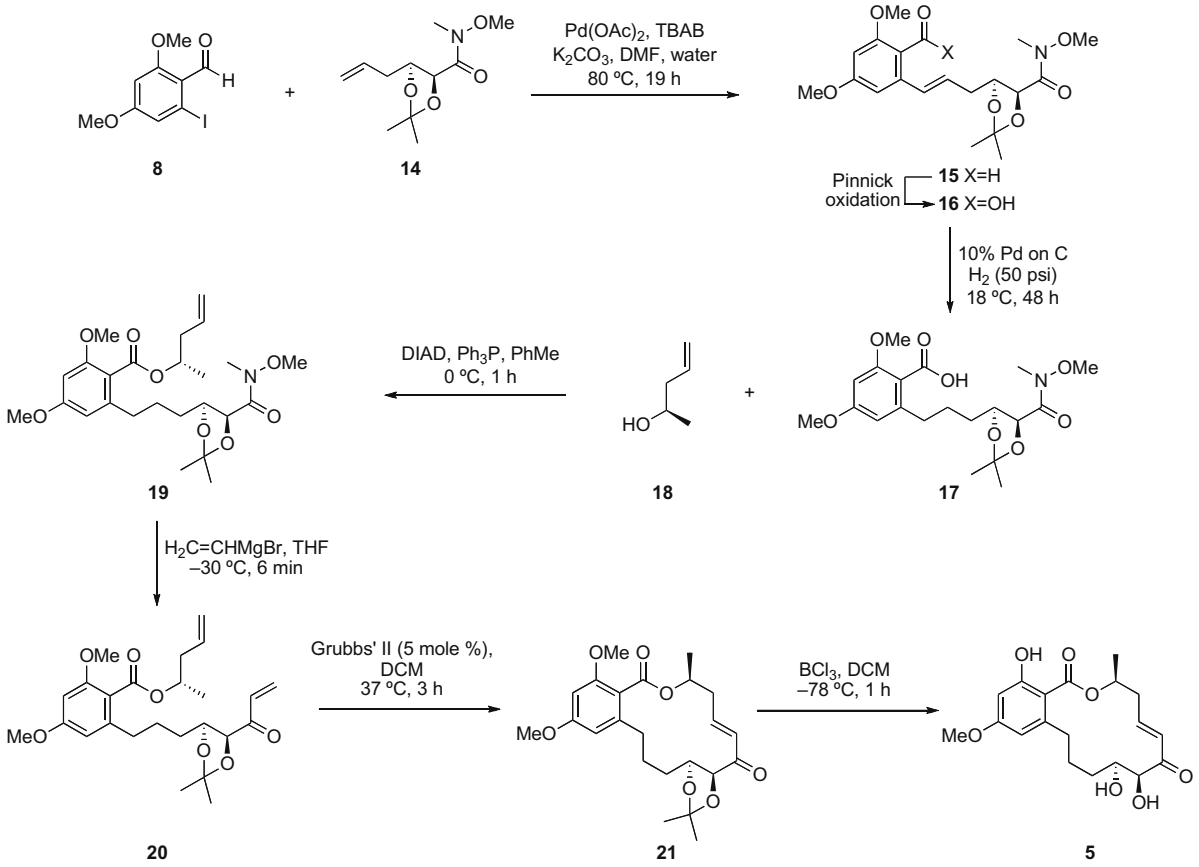


Figure 1. Structure of compound **5** with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



Scheme 3.

All the spectral data derived from compound **5** were entirely consistent with the assigned structure,[21] but the final confirmation of this was secured through a single-crystal X-ray analysis of its chloroform solvate.[22] The derived ORTEP is shown in Figure 1. No spectral data derived from the natural product L-783,290 have been published and, thus far, our various efforts to secure these have been unsuccessful. As such, we have been unable to make relevant comparisons between the two sets of data.

The results of the biological evaluation of compound **5** and the adaptation of the protocols described here to the synthesis of other RAL's will be described in due course.

Acknowledgements

We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support.

Supplementary data

Supplementary data (experimental procedures and product characterization for compounds **5**–**8**, **11**–**17**, **19** and **20**, as well as the X-ray crystal data for compounds **5** and **14**, are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.067.

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17. The conditions employed were essentially those of Jeffery (Jeffery, T. *Tetrahedron* **1996**, *52*, 10113).
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21. Selected spectral data derived from compound **5**: mp 127.5–136.5 °C; $[\alpha]_D$ +9.7 (*c* 0.23, $CHCl_3$); ^1H NMR (800 MHz, CD_2Cl_2) δ 11.83 (s, 1H), 7.00 (m, 1H), 6.37 (m, 3H), 5.57 (m, 1H), 4.68 (s, 1H), 3.96 (s, 1H), 3.80 (s, 3H), 3.06 (t, J = 12.8 Hz, 1H), 2.84 (br s, 1H), 2.54 (m, 2H), 1.71 (br s, 2H), 1.62 (s, 1H), 1.45 (d, J = 6.1 Hz, 3H), 1.30 (m, 1H) (signals due to two protons not observed); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 199.3, 171.4, 166.3, 164.7, 147.7, 143.8, 131.5, 109.5, 104.9, 99.3, 77.4, 73.3, 71.3, 55.7, 38.0, 36.2, 32.8, 26.9, 19.2; IR ν_{max} 3347, 2938, 1695, 1642, 1615, 1353, 1316, 1250, 1202, 1161, 1131, 1111, 1089, 1045, 995 cm^{-1}; MS *m/z* (EI, 70 eV) 364 ($M^{+\cdot}$, 17%), 221 (80), 202 (43), 193 (58), 192 (100), 177 (48), 164 (75); HRMS Found $M^{+\cdot}$, 364.1532. $C_{19}H_{24}O_7$ requires $M^{+\cdot}$, 364.1522.
22. X-ray crystal data for compound **5** (CCDC no. 751602) can be found in the Supplementary data.