

Concise Strategy to the Core Structure of the Macrolide Queenslandon

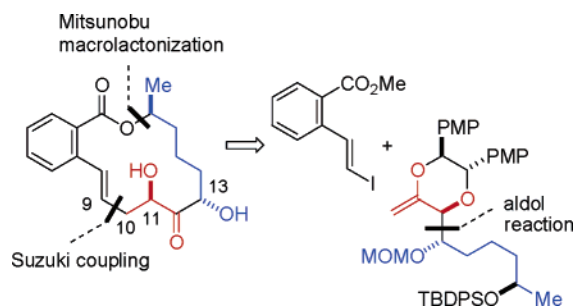
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ABSTRACT



The fully functionalized core structure of the macrolactone queenslandon was prepared using a novel strategy consisting of a glycolate aldol reaction and hydroboration of the derived enol ether 17 followed by Suzuki cross-coupling with an iodostyrene. After conversion of the cross-coupling product to the seco acid 22, Mitsunobu macrolactonization and protecting group manipulations led to the queenslandon model 5.

Benzolactones represent an important subclass among the polyketides.^{1–3} The ones that feature an acetate as a starter unit normally contain a 14-membered macrolactone. The benzoic acid part in these compounds is the result of an intramolecular aldol condensation. Often a double bond or a ketomethylene function is located next to the aryl ring. The aliphatic sector is generally functionalized with hydroxyl or keto groups. Several benzolactones are depicted in Figure 1. Even though their structures are quite similar, each of them displays a characteristic and unique type of biological activity. Thus, the benzolactone core clearly is an important privileged structure. Queenslandon (**1**) was isolated from the strain *Chrysosporium queenslandicum* IFM51121.⁴ This macrolactone showed distinct activity against fungi but was

devoid of antibacterial activity. The classical benzolactone, the fungal metabolite zearalenone (**2**), shows oestrogenic activity.⁵ The antitumor activity seems to be connected to

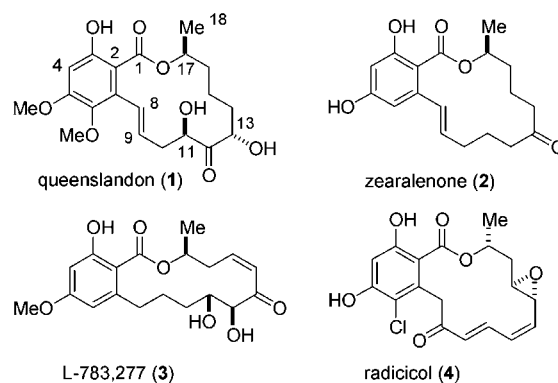


Figure 1. Some typical 14-membered benzolactones with a methyl substituent.

(1) Zotchev, S. B.; Stepanchikova, A. V.; Sergeiko, A. P.; Sobolev, B. N.; Filimonov, D. A.; Poroikov, V. V. *J. Med. Chem.* **2006**, *49*, 2077–2087.

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the inhibition of cyclin-dependent kinases. The resorcylic acid lactone L-783,277 (**3**), a fungal metabolite as well, was reported to be a selective inhibitor of MEK, a threonine/tyrosine specific kinase resulting in antitumor activity.⁶ With regard to the biological activity, the unsaturated ketone is important. Another prominent member of the benzolactone family of natural products, radicicol (**4**), confers its antitumor activity through inhibition of the chaperone HSP90.⁷ The related pochonins seem to target HSP90 as well, inducing antiviral and antiparasitic activity.⁸ It follows that the benzolactones are important lead structures for the search of novel antitumor compounds.⁹ In particular, structure–activity studies might illuminate key factors that make out the difference in the binding of a certain kinase.¹⁰

In this paper, we describe the synthesis of the queenslandon analogue **5** based on the key bond-forming reactions indicated in Figure 2. Major challenges that we recognized

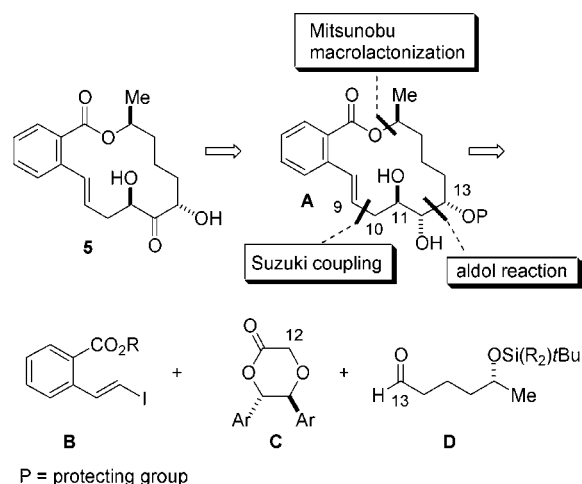


Figure 2. Key retrosynthetic disconnections for the queenslandon model compound **5**.

from a synthetic point of view were the connection of the aliphatic chain to the aryl ring and the creation of the carbohydrate-like sector. For the macrolactonization, a ring-closing metathesis (RCM) strategy might be considered.^{11,12} However, steric hindrance around the styrene double bond

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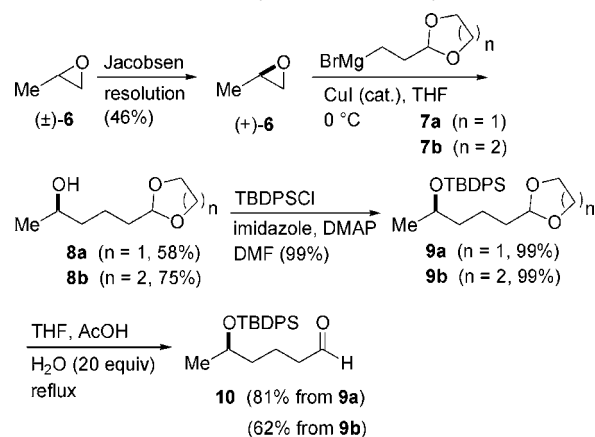
(11) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911–939.

(12) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

could make this strategy less ideal.^{13,14} Instead, we opted for a Mitsunobu macrolactonization strategy. As a further key disconnection, a Suzuki coupling at the vinylic position (C9–C10) was envisioned.¹⁵ The necessary alkyl-borane, in turn, should result from a diastereoselective hydroboration of an exocyclic enol ether. The stereocenter at C13 would be the result of a glycolate aldol reaction.

The aldehyde **10** was synthesized starting from racemic propylene oxide [(±)-**6**] in four steps (Scheme 1). Jacobsen

Scheme 1. Synthesis of Aldehyde **10**



resolution furnished the (*R*)-epoxide (+)-**6** in 99% ee.¹⁶ Opening of this epoxide with either the Grignard reagent **7a** or **7b** in the presence of catalytic amounts of CuI led to the corresponding secondary alcohols **8a** and **8b**, respectively. The hydroxy acetal **8a** turned out to be rather sensitive toward internal transacetalization. It was therefore immediately protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl). Hydrolysis of the acetal in compound **9a** provided aldehyde **10**.¹⁷ The six-membered acetal **8b** could be isolated in higher yield (75% vs 58%) and found to be more stable. However, cleavage of the acetal function on the silyl-protected **9b** was less efficient.

The Andrus glycolate **14** was prepared essentially according to the literature from *p*-methoxybenzylalcohol, but one step was slightly modified (Scheme 2).^{18,19} Thus, we found that the Wittig–Horner condensation of phosphonate **11** with anisaldehyde using NaOMe as a base gave only low yields of the stilbene **12** irrespective of the solvent (DMF or THF).

(13) For the synthesis of zearalenone via RCM, see: Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990–7995.

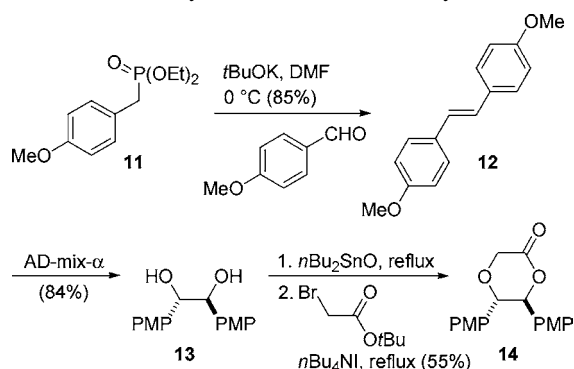
(14) For the synthesis of zearalenone via intramolecular Stille coupling, see: Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883–2894.

(15) For recent reviews, see: (a) Suzuki, A. *Chem. Commun.* **2005**, 4759–4763. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

(16) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

(17) For the synthesis of a related aldehyde from lactate, see: Haynes, R. K.; Lam, W. W. L.; Yeung, L.-L.; Williams, I. D.; Ridley, A. C.; Starling, S. M.; Vonwiller, S. C.; Hambley, T. W.; Lelandais, P. *J. Org. Chem.* **1997**, *62*, 4552–4553.

Scheme 2. Synthesis of the Andrus Glycolate **14**

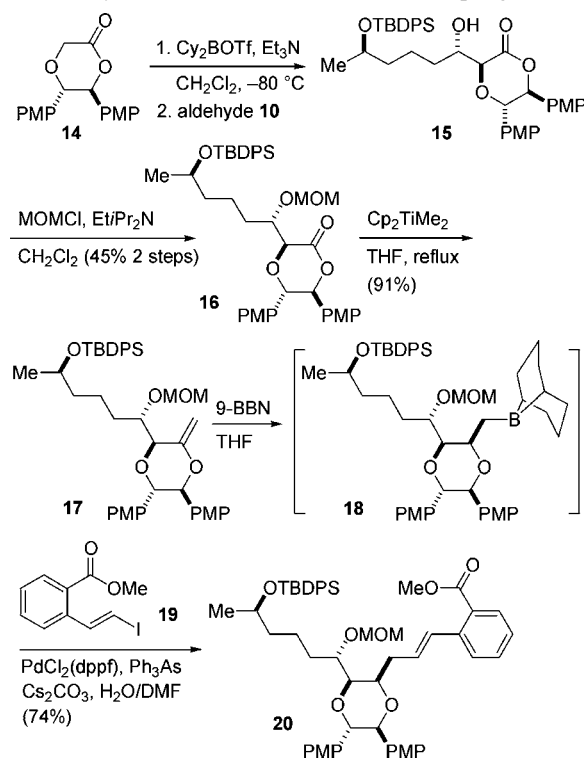


A much better yield could be realized with potassium *tert*-butoxide as base. Dihydroxylation²⁰ of alkene **12** using AD-mix- α led to diol **13**. Reaction of diol **13** with di-*n*-butyltin oxide followed by treatment with *tert*-butyl bromoacetate gave the glycolate **14**.

Aldehyde **10** and glycolate **14** were combined via an aldol reaction employing the dicyclohexylboron enolate of **14** in the presence of Et₃N forming the anti adduct **15** with high selectivity (9:1 dr) (Scheme 3).¹⁸ The aldol product **15** is somewhat prone to retro aldol reaction. Therefore, its secondary alcohol function was immediately protected as a MOM ether. Other attempts at protecting the alcohol of **15** (TBSOTf or TIPSOTf and base, BnBr and Ag₂O) were not successful. Nevertheless, this route allowed for the convenient preparation of **16** in gram amounts. The substrate for the key Suzuki cross-coupling reaction was prepared in high yield by Tebbe olefination of dioxanone **16** using Petasis conditions.²¹ Following addition of 9-BBN to the enol ether **17**, the intermediate borane **18** was subjected to a palladium-catalyzed coupling reaction with iodostyrene **19**.²² The latter was obtained by a Takai reaction^{23,24} with an *E/Z*-ratio of 5:1.²² Applying an excess (2 or more equiv) of **19** in the Suzuki coupling with **18** delivered the alkene **20** enriched in the desired *E*-isomer (*E/Z* > 20:1).

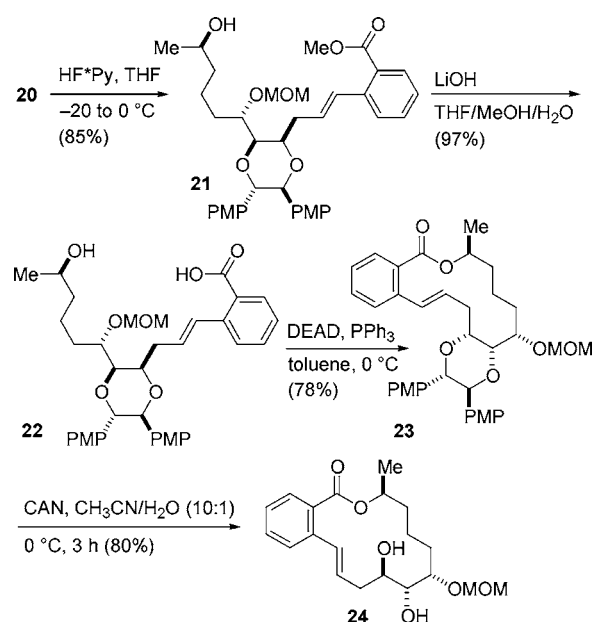
To reach the hydroxy acid **22**, the silyl ether of **20** was cleaved with an excess of the HF/pyridine complex at -20 °C in THF (Scheme 4). TBAF in THF, even at reflux, left the starting material unchanged. Saponification of the methyl

Scheme 3. Aldol Reaction, Protection, Tebbe Olefination, Hydroboration, and Suzuki Cross-Coupling



ester with LiOH at reflux proceeded essentially in quantitative yield. Macrolactone formation of hydroxy acid **22** under Mitsunobu conditions (DEAD, Ph₃P, toluene, 0 °C) gave rise to lactone **23** in high yield (78%). Most likely, conformational constraints on the backbone, imposed by the dioxane ring, facilitate formation of the macrocycle. Cleavage of the

Scheme 4. Synthesis of Macrolactone **24** via Mitsunobu Macrolactonization



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(19) See Supporting Information.

(20) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

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(24) Auge, J.; Boucard, V.; Gil, R.; Lubin-Germain, N.; Picard, J.; Uziel, J. *Synth. Commun.* **2003**, *33*, 3733–3739.

dioxane in macrolactone **23** could be accomplished with excess ceric ammonium nitrate in a CH₃CN/H₂O mixture at 0 °C resulting in diol **24**.²²

Crystallization of lactone **24** from methanol provided crystals suitable for X-ray analysis. An ORTEP plot of **24** is shown in Figure 3 indicating the configurations at the chiral

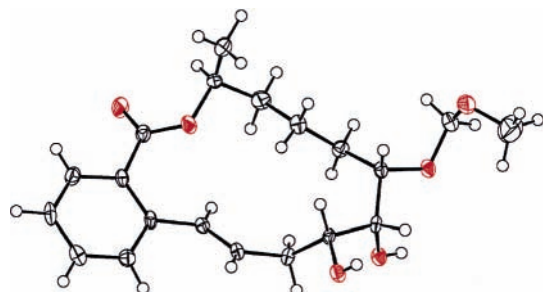


Figure 3. X-ray structure of macrolactone **24**.

centers and the conformation of the macrocycle. The X-ray structure additionally proved the facial selectivity of the hydroboration step (**17** → **18**), originally inferred from NMR data.

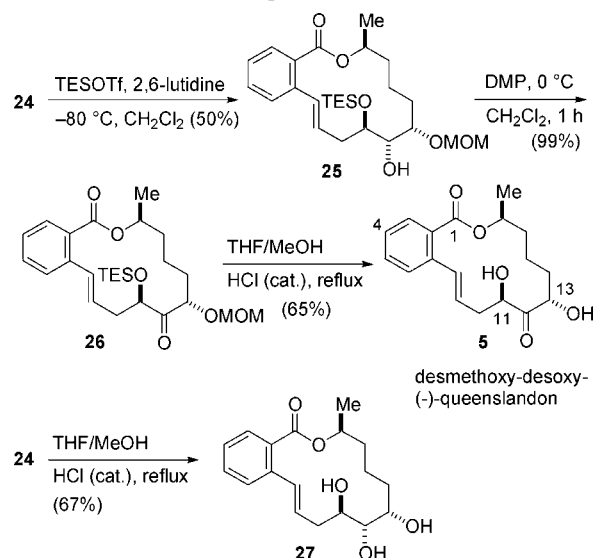
As a final challenge, differentiation of the two secondary hydroxy functions remained. A related transformation was described by Kirschning et al. in their total synthesis of tonantzitlolone where two outside hydroxyl groups of a triol were protected with triethylsilyl chloride (TESCl) and imidazole as base.²⁵ In the case at hand, the monosilylation of **24** with TESCl was indeed possible but the reaction was rather slow, taking up to three weeks. Using the more reactive TESOTf (1.5 equiv), 2,6-lutidine as base, and low temperature (−50 °C), we obtained the desired silyl ether **25** in 50% yield within 12 h (Scheme 5). Besides ether **25**, some starting material plus a double protected derivative were present in the reaction mixture. Subsequent oxidation of alcohol **25** with Dess–Martin periodinane gave ketone **26**. Global deprotection of **26** under acidic conditions provided the queenslandon analogue **5**. Additionally, deprotection of **24** led to triol **27**.

The regiochemistry in the selective ether formation was inferred from the COSY NMR spectrum of the final compound, dihydroxyketone **5**. Most supportive in the assignment was the absence of a cross-peak between 11-H and 13-H (see Supporting Information). Rather prominent correlations were seen for the methine H's, 11-H and 13-H, with their neighboring methylene groups. The keto group resonates at $\delta = 212.5$ ppm in the ¹³C NMR spectrum. Preliminary cytotoxicity assays (L929 mouse fibroblast cells) on macrolactone **5** showed an IC₅₀ of 40 $\mu\text{g mL}^{-1}$. At the same concentration, **27** was less active, reaching an inhibition of 40%.²⁶

In summary, we developed an efficient asymmetric synthesis of macrolactone **5**, featuring the complete aliphatic

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Scheme 5. Selective Monoprotection, Oxidation, and Global Deprotection



sector of queenslandon (**1**). The synthesis involved 16 steps and proceeded with good overall yield from racemic propylene oxide (**6**). All chiral centers were essentially obtained via catalytic methods (Jacobsen resolution, ADH). We also note that the chiral dioxane moiety served multiple purposes as a chiral auxiliary in the aldol reaction, then as the controller in the diastereoselective hydroboration step, and as a conformational constraint during the Mitsunobu macrolactonization. The same strategy should allow for the preparation of further queenslandon analogues and the natural product itself.

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Note Added after ASAP Publication: Mitsunobu macrolactonization was incorrectly identified as Yamaguchi macrolactonization in the version published ASAP November 8, 2006; the corrected version was published ASAP November 10, 2006.

Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) These assays were performed in the group of Dr. Florenz Sasse, Helmholtz-Zentrum für Infektionsforschung GmbH, Chemische Biologie, Inhoffenstrasse 7, 38124 Braunschweig, Germany.