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Fast and efficient synthesis of the complete LL-Z1640-2 framework

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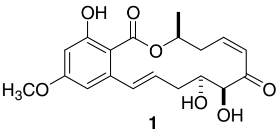
Abstract—The convergent synthesis of the complete LL-Z1640-2 framework has been completed. This fast and efficient approach provides flexible access into the resorcyclic lactones.

TAK1 is a member of the mitogen-activated protein kinase kinase kinase (MAPKKK) family that phosphorylate and activate MKK3, MKK4, MKK6 and MKK7 MAPKKs, which in turn activate the c-Jun N-terminal kinase (JNK) and p38 MAPKs.[1] It has also been recently demonstrated that TAK1 activates IkB kinases (IKKs), ultimately leading to activation of the transcription factor NF-κB.[2]

A significant amount of work has been devoted in trying to understand TAK1 and its role in the areas of cell apoptosis, and tumour necrosis, as well as on proinflammatory diseases. Several lines of evidence tend to suggest that TAK1 is a key participant in proinflammatory signalling pathways, i.e., by activating both JNK/p38 MAPKs and IKKs in the interleukin 1 (IL-1) signalling pathway.[3] The mechanism by which the IL-TAK1 signalling pathway is positively and negatively regulated remains poorly understood, and their physiological functions remain to be clarified. However, it is believed that selective inhibition of TAK1 might be effective in preventing inflammation and tissue destruction promoted by proinflammatory cytokines.[4]

As a part of our biological chemistry programme in understanding inflammatory responses, we were interested in the development of a potent and selective set of chemical genetic probes that would allow us to understand better the role of TAK1.

LL-Z1640-2 (also known as 5*Z*-7-oxo-zeaenol and C292) (**1**) was isolated in 1978 from the culture broth of fungal strain f6024.[5] Although it was originally classified as an anti-protozoan agent, it was not until 1999 that its cytokine release inhibiting activity was discovered.[6] LL-Z1640-2 (**1**) has been shown to be a selective protein tyrosine kinase inhibitor, not inhibiting either protein kinase A (PKA) or protein kinase C (PKC).[7]



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Significantly, preliminary data suggest that LL-Z1640-2 (**1**), can selectively and irreversibly inhibit the kinase activity of purified TAK1 at very low concentrations (IC_{50} 8.1 nM). Furthermore, **1** had no effect on the kinase activity of other members of the MAPKKK family (MEKK1 and ASK1).[7] In addition LL-Z1640-2 (**1**) has also been reported as having significant activity versus tumour necrosis factor-alpha (TNF-α) production in cells with an IC_{50} of 6 nM.[6]

LL-Z1640-2 (**1**) is structurally related to the 14-membered macrocyclic lactones hypothemycin (**2**), 87-250904-F1 (**3**), zeaenol (**4**), 7-oxo-zeaenol (**5**), radicicol (**6**), and various simpler zearalanone and zearalanols (Fig. 1). However, **1** is unique amongst the resorcyclic lactones in its potency in targeting TAK1, raising the prospect of becoming a truly selective starting point in chemical genetics research.[8]

Keywords: LL-Z1640-2; Resorcyclic lactones; Anti-inflammatory.

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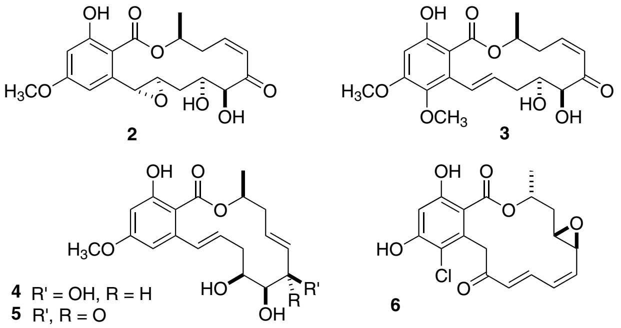


Figure 1.

Although there has been a significant amount of work dedicated to the synthesis of radicicol **6** by Danishefsky and co-workers, efforts towards LL-Z1640-2 (**1**), have been rather limited. This lack of synthetic interest has translated into a lack of chemical genetic probes through which the active site of TAK1 could be explored and understood.[9,10]

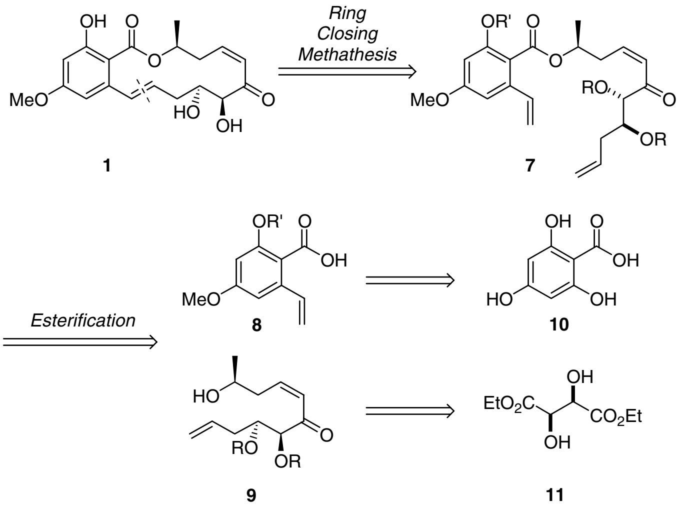
Herein, we report a flexible and efficient approach to the synthesis of the complete LL-Z1640-2 (**1**) framework and its C9 epimer, which molecular modelling should be useful in helping elucidate the conformation of LL-Z1640-2 (**1**) within the TAK1 active site. We believe that our robust and cost effective approach provides the foundations which will allow these compounds to be considered as realistic chemical biological leads for the first time.

Our convergent retrosynthetic analysis called for the cleavage of the macrocyclic ring at the ester functionality and the benzylic double bond, generating the vinyl benzoic acid **8** and C1–C10 alcohol **9** (Scheme 1).

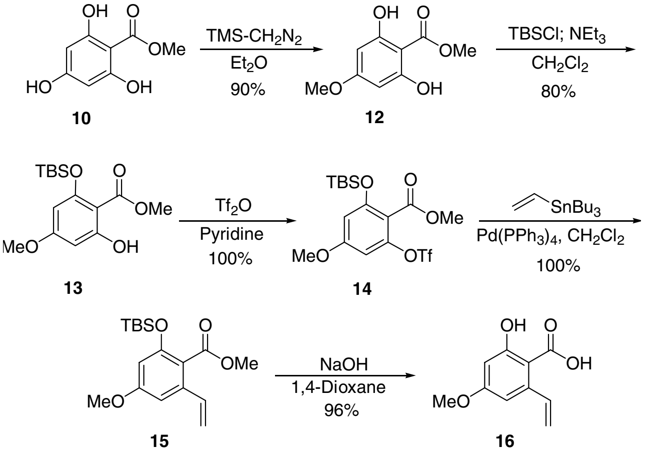
The synthesis of the vinyl benzoic acid unit **8** began with commercially available methyl 2,4,6-trihydroxybenzoate **10** which was methylated selectively at the C4 position to afford the desired diol **12** in excellent yield.[11] Monosilylation of diol **12** proceeded in good yield to produce the TBS silyl ether **13**, which was then converted to the corresponding triflate **14** in quantitative yield (Scheme 2).

A Stille coupling of the newly generated aryl triflate with vinyltributyl tin proceeded in excellent yield to afford the desired vinyl benzene **15**. Finally, saponification of the methyl ester proceeded with concomitant desilylation to generate the free benzoic acid **16** in near quantitative yield.

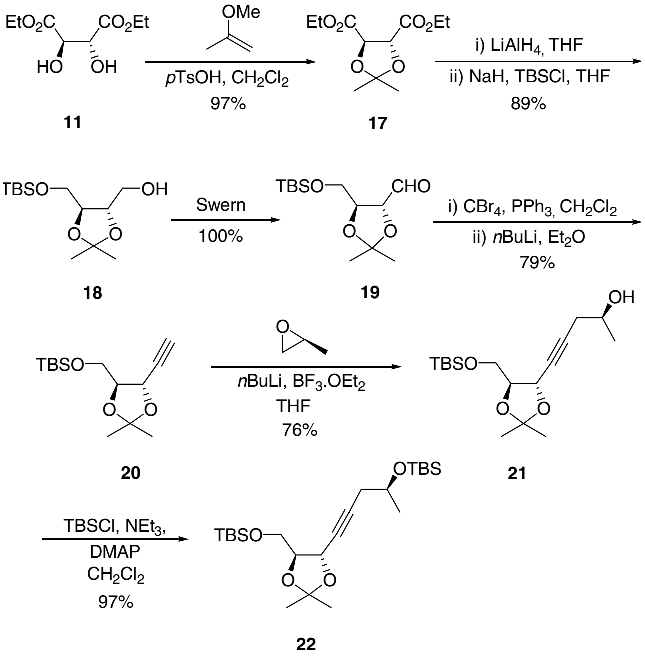
Our synthesis of the aliphatic C1–C10 unit began with readily available (L)-(+)-diethyl tartrate **11** which was protected as the dimethyl ketal **17**. Reduction of the diester functionality generated the corresponding diol unit, which upon selective hydroxyl group silylation provided TBS ether **18** in excellent yield.[12] Swern oxidation of alcohol **18** proceeded in quantitative yield to generate the expected aldehyde **19**, which upon treatment under Corey–Fuchs olefination conditions gave the desired alkyne **20** in high yield. The newly generated alkyne **20** was then alkylated with (*S*)-propylene oxide under



Scheme 1.



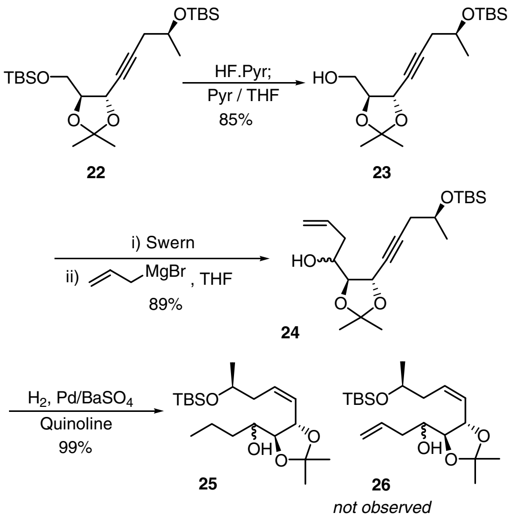
Scheme 2.



Scheme 3.

highly activated conditions to afford the desired internal alkynol **21** as a single diastereomer in good yield. Silylation proceeded efficiently to generate the bis-TBS silyl ether **22** in very high yield (Scheme 3).

The last steps of the synthesis of the C1–C10 unit began with selective deprotection of the primary TBS silyl ether of alkyne **22** under carefully monitored conditions to afford the desired primary alcohol **23** in good yield. Rewardingly, a one-pot oxidation–allylation sequence proceeded to generate homoallylic alcohol **24** as a mixture of diastereomers (1:1) in excellent yield over the two steps (Scheme 4). No attempt was made to control the stereochemistry of allylation as we wanted to access both LL-Z1640-2 and its C9 anomer for biological evaluation.



Scheme 4.

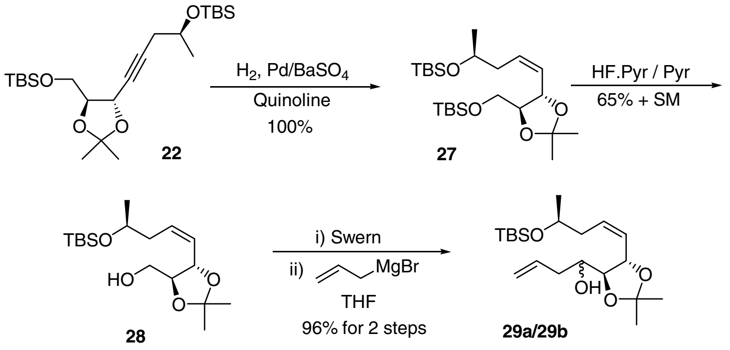
Having successfully completed the synthesis of the C1–C10 unit, we focused our attention on the conversion of the alkyne unit into the *Z*-alkene functionality present in LL-Z1640-2 (**1**). Unfortunately, despite repeated experimentation, all hydrogenation attempts failed to provide us with the desired diene unit **26**, affording instead the over-reduced alkane **25**. We believe that this over-reduction could be attributed to the presence of the free homoallylic alcohol unit.

The loss of the key terminal alkene functionality during the introduction of the internal alkene moiety prompted us to re-evaluate the synthetic route. Our modified approach to the synthesis of the C1–C10 unit of LL-Z1640-2 began with the previously obtained bis-TBS ether **22**, which was selectively reduced to generate the *Z*-olefin **27** in quantitative yield and with complete stereocontrol. Selective TBS group removal then provided primary alcohol **28** in good yield. A similar one-pot Swern oxidation–allylation procedure to that used previously proceeded cleanly and in excellent yield to complete the syntheses of the C1–C10 fragments of LL-Z1640-2 and 9-*epi*-LL-Z1640-2, **29a** and **29b**, respectively (Scheme 5).

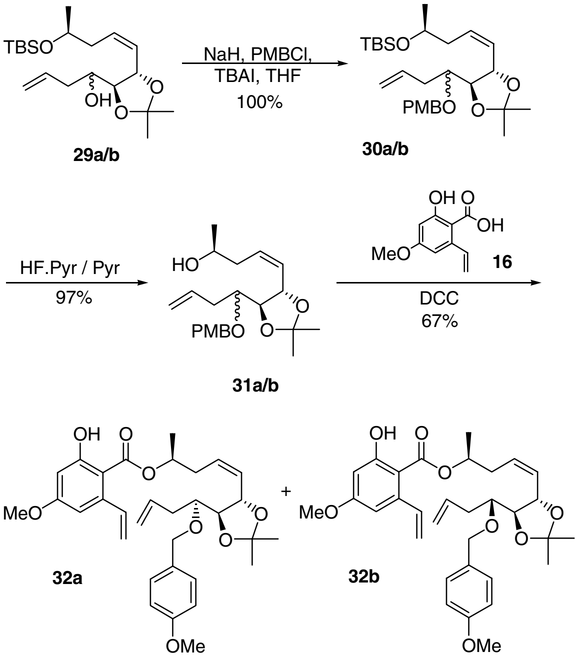
Having successfully introduced both alkene units with complete stereocontrol, we decided to introduce the remaining units of the LL-Z1640-2 framework. Hence, alkenes **29a/29b** were protected to give the corresponding PMB ethers **30a/b** in quantitative yield. Careful removal of the secondary TBS silyl ether afforded secondary alcohols **31a/b** required for the esterification (Scheme 6).

Gratifyingly, reaction of alcohols **31a/b** with the previously described vinyl benzoic acid **16** proceeded cleanly to generate esters **32a** and **32b** incorporating the entire LL-Z1640-2 (**1**) and the 9-*epi*-LL-Z1640-2 frameworks in good overall yields.

In conclusion, we have demonstrated a fast, high yielding and flexible approach to the synthesis of LL-Z1640-2



Scheme 5.



Scheme 6.

(**1**) and its C9-epimer taking advantage of two-directional chain functionalisation and of an efficient synthetic pathway. The completion of the synthesis as well as the results of our biological assessment of all the intermediates will be reported in due course.

Acknowledgements

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