A ring-closing metathesis (RCM)-based approach to mycolactones A/B

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The total synthesis of the mycobacterial toxins mycolactones A/B (1 a/b) has been accomplished based on a strategy built around the construction of the mycolactone core through ring-closing metathesis. By employing the Grubbs second-generation catalyst, the 12-membered core macrocycle of mycolactones, with a functionalized C2 handle attached to C11, was obtained in 60-80 % yield. The C-linked upper side chain (comprising C12-C20) was completed by a highly efficient modified Suzuki coupling between C13 and C14, while the attachment of the C5-O-linked polyunsaturated acyl side chain was achieved by Yamaguchi esterification. Surprisingly, a diene containing a simple isopropyl group attached to C11 could not be induced to undergo ring-closing metathesis. By employing fluorescence microscopy and flow cytometry techniques, the synthetic mycolactones A/B (1 a/b) were demonstrated to display similar apoptosis-inducing and cytopathic effects as mycolactones A/B extracted from Mycobacterium ulcerans. In contrast, a simplified analogue with truncated upper and lower side chains was found to be inactive
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