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Total Synthesis of (−)-Okilactomycin

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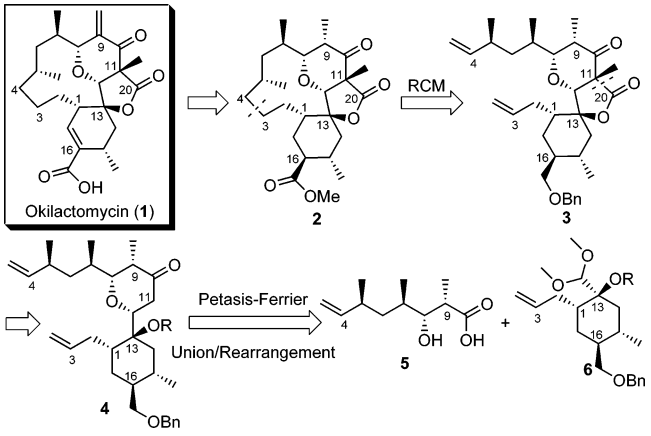
In 1987, Imai and co-workers reported the isolation and structure of (+)-okilactomycin (**1**, Scheme 1), a novel polyketide antitumor antibiotic isolated from a bioactive filtrate of *Streptomyces griseoflavus*. The structure, comprising a highly functionalized cyclohexene ring complete with a spirocenter and a 2,6-*cis*-tetrahydropyranone moiety, appended in a 13-membered ring,[1] was initially elucidated via a combination of NMR experiments. The connectivity and relative stereochemistry were subsequently confirmed by X-ray analysis; however, the absolute stereochemistry remained undefined. Importantly, (+)-okilactomycin exhibits significant in vitro cytotoxicity against the human cell lines P388 and lymphoid leukemia L1210 (IC_{50} = 0.09 and 0.037 μg/mL respectively). While this antitumor antibiotic has attracted some interest in the synthetic community,[2] a total synthesis has not, as yet, been achieved. Herein, we disclose the first total synthesis of (−)-**1**, the antipode of the natural product.

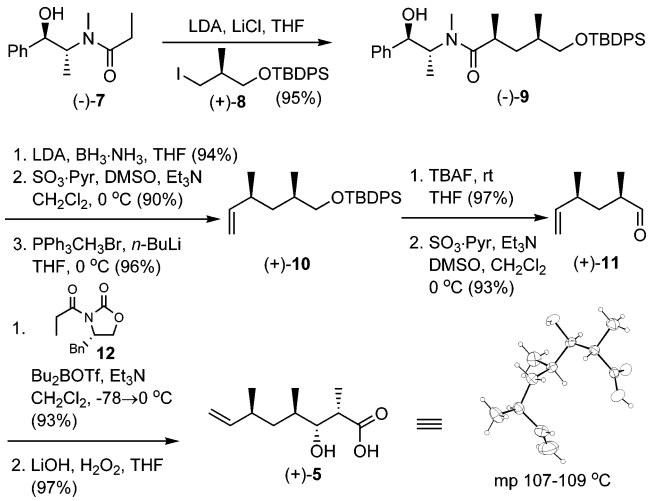
Scheme 1



From the retrosynthetic perspective, we envisioned **1** to be constructed via oxidative elimination of a bis-selenide derived from **2** (Scheme 1), which in turn would arise from **3**, exploiting ring closing metathesis (RCM),[3] followed by oxidation state adjustment. Lactone **3** would in turn be generated from an orthogonally protected tetrahydropyranone **4**, the latter constructed from β-hydroxy acid **5** and dimethyl acetal **6**, exploiting the powerful Petasis−Ferrier union/rearrangement[4] tactic recently developed in our laboratory (vide infra).[5]

Synthesis of **5** (Scheme 2) began via diastereoselective alkylation of the Myers pseudoephedrine-derived auxiliary **7**[6] with known iodide (+)-**8**[7] to yield amide (−)-**9** as a single diastereomer. Reduction[6] followed by oxidation provided an aldehyde, which upon methylenation led to alkene (+)-**10**. Removal of the TBDPS group and oxidation then furnished aldehyde (+)-**11**, which upon a diastereoselective Evans aldol reaction[8] with oxazolidinone **12**, followed by hydrolytic removal of the auxiliary, afforded β-hydroxy acid (+)-**5**. The overall yield for the eight-step sequence was 63%; the structure and relative stereochemistry of (+)-**5** were verified by X-ray analysis.

Scheme 2



Construction of acetal **6** (Scheme 3) began with a diastereoselective Rawal Diels−Alder reaction[9] between diene (+)-**13** and methyl crotonate, followed by reduction to provide carbinol (+)-**14**. Protection of the primary alcohol as the benzyl ether and, in turn, hydrolytic removal of the auxiliary mediated by HF furnished enone (+)-**15**, which upon 1,4-reduction and capture of the resulting enolate with $PhNTf_2$ yielded (−)-**16**.[10] A Pd-catalyzed carbonylation,[11] followed by diastereoselective allylation,[12] next led to secondary alcohol (+)-**17** as the major diastereomer (dr 15:1), thereby setting the stage for a pivotal anion accelerated oxy-Cope rearrangement[13] to introduce the requisite α-allyl substituent at C(1). Gratifyingly, this reaction proceeded with excellent stereocontrol, presumably via a chair-like transition state to furnish an enolate which was methylated (Me_2SO_4) to provide enol ether **18** as a mixture of *E*/*Z* isomers (2:1). Upon exposure to *m*-CPBA in methanol, a Rubottom-like oxidation[14] led to α-hydroxylation from the more accessible axial face followed by generation of the corresponding hydroxy dimethyl acetal, which was subsequently converted to 2-napthylmethyl ether[15] (+)-**6a**, a single acetal with complete orthogonal protection (vide infra).

Turning to the Petasis−Ferrier union/rearrangement tactic to construct the tetrahydropyranone, we quickly discovered, initially with **6b**,[16] that the terminal olefin preferentially undergoes an intramolecular Prins cyclization[17] (cf. **19** and **20**) with the acetal during attempted TMSOTf-promoted condensation with the bis-silylated derivative of hydroxyl acid (+)-**5**, the first or union step of the Petasis−Ferrier sequence (Scheme 3). To combat the Prins process, we masked the olefin as the bromo derivative, (+)-**21**, prepared by addition of the Schwartz reagent to (+)-**6a** followed by NBS.[18] Pleasingly, the Petasis−Ferrier tactic proceeded to furnish

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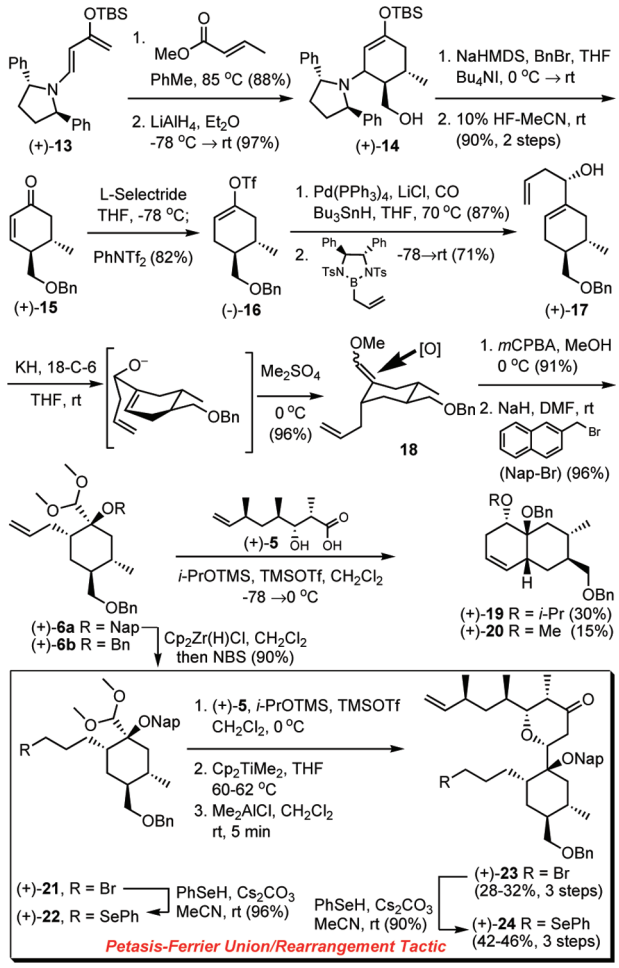
(+)-**23**, albeit in modest yield (28−32%) over the three steps. Not withstanding the modest yield, this sequence constitutes the first example of a Petasis−Ferrier union involving an acetal, possessing a sterically demanding α-quaternary center. The requisite terminal olefin could then be regenerated via conversion to selenide (+)-**24**, followed by oxidative elimination. Although the bromide proved to be a viable Petasis−Ferrier partner, we subsequently discovered that selenide (+)-**22**, prepared by displacement of bromide (+)-**21**,[19] was the preferred Petasis−Ferrier substrate, given that the bromide undergoes competitive elimination during the Petasis olefination, resulting in the accumulation of several byproducts.

Scheme 3

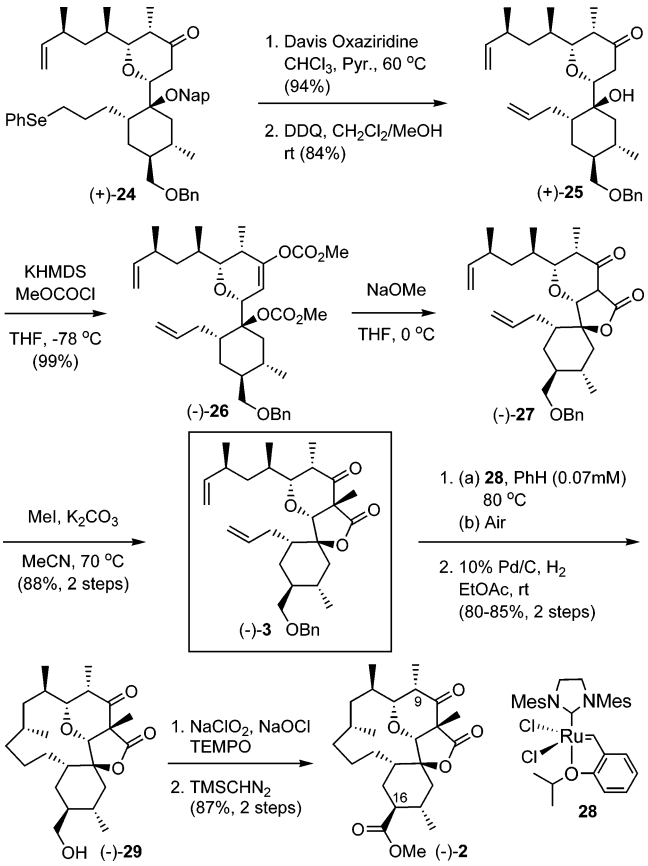


From the perspective of material advancement, the Petasis−Ferrier tactic employing (+)-**22** proved quite effective; union with (+)-**5** readily furnished the corresponding dioxanone (Scheme 3), which upon Petasis−Tebbe methylenation[20] and subsequent rearrangement of the somewhat unstable enol-acetal furnished (+)-**24** as a single diastereomer in 42−46% for the three steps.

Continuing with the synthesis, oxidative elimination[21] of the selenide (Scheme 4), followed by removal of the orthogonal 2-napthylmethyl group employing DDQ,[22] led to carbinol (+)-**25**, the requisite intermediate envisioned for construction of lactone **3**. To this end, biscarbonate (−)-**26** was subjected to chemoselective methanolysis to form an intermediate sodium enolate, derived from the enol carbonate, which in turn undergoes cyclization with the tertiary carbonate to furnish lactone (−)-**27** as a single diastereomer.[23] The required RCM precursor (−)-**3** was then generated by installation of the C(11) methyl group (MeI/K_2CO_3).[24]

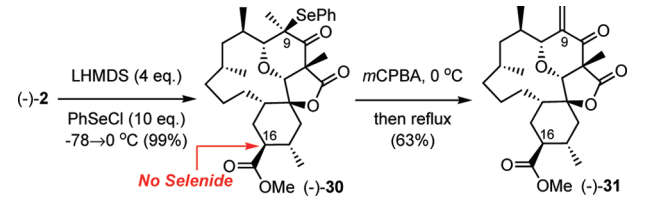
Pleasingly, the RCM reaction, employing the Hoveyda−Grubbs second generation catalyst[25] followed by hydrogenation of the derived *cis*-alkene (J = 10 Hz) produced macrocycle (−)-**29** in 80−85% yield for the two steps. To achieve optimal yields, destruction of the RCM catalyst by exposure of the reaction mixture to "air" prior to concentration proved critical to avoid competitive polymerization. Oxidation (TEMPO) to the corresponding acid, followed by esterification, then furnished (−)-**2**, the requisite precursor for bis-selenation and oxidative elimination[26] to complete construction of okilactomycin (**1**).

Scheme 4



Unexpectedly, however, all attempts to produce the bis-selenide led only to monoselenide (−)-**30** (Scheme 5). Resubjection of the monoselenide to a wide variety of selenation conditions resulted only in the recovery of starting material and/or complete decomposition. Surprisingly, during these efforts, epimerization at C(16) did not occur, suggesting our inability to access the enolate at C(16), presumably due to steric hindrance arising from the macrocycle. Oxidative elimination of (−)-**30** did provide exclusively dihydrookilactomycin methyl ester (−)-**31** in 63% yield.

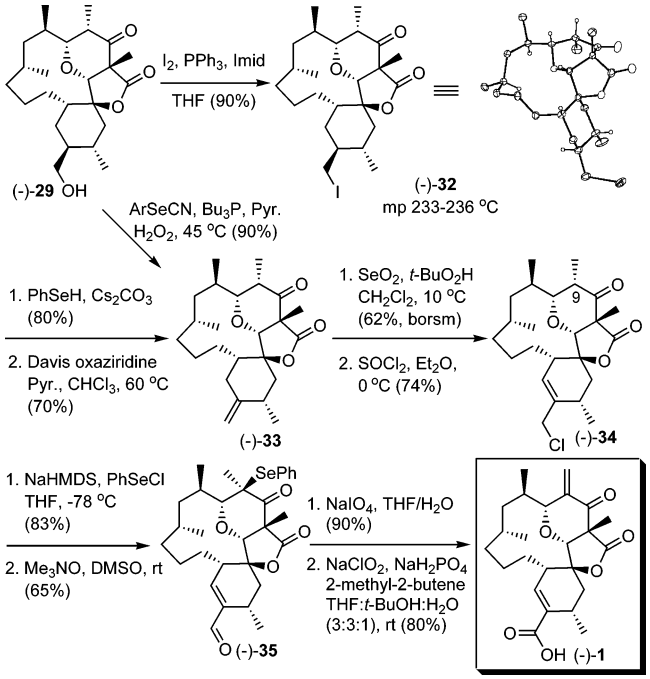
Scheme 5



Undaunted, the decision was made to undertake an alternate approach to install the C(16)−C(17) olefin. Toward this end, alcohol (−)-**29** was converted to the exocyclic alkene (−)-**33** in three steps (Scheme 6). X-ray analysis of iodide (−)-**32** established the structure, thereby confirming the connectivity and stereochemistry.

We later established that (−)-**29** could be converted directly to (−)-**33** in one step via the Grieco−Nishizawa protocol.[27] Allylic oxidation[28] of (−)-**33** next led to a mixture (2.5:1) of the desired secondary allyl alcohol (62%, borsm), along with the regioisomeric tertiary allylic alcohol. Rearrangement of the former with $SOCl_2$[29] furnished allylic chloride (−)-**34**, securing the requisite trisubstituted C(16)−C(17) olefin required for okilactomycin (**1**). Installation of a phenyl selenide at C(9), followed by Ganem oxidation,[30] provided aldehyde (−)-**35**, which upon selenoxide elimination and Pinnick oxidation[31] completed construction of (−)-okilactomycin (**1**),[1] spectroscopically identical in all respects (^{1}H, ^{13}C, HRMS) to an authentic sample obtained from the natural source,[1a] with exception of the chiroptic properties {$[\alpha]^{20}_D = -37$ ($c = 0.03$, MeOH); lit.[1a] $[\alpha]^{20}_D = +34$ ($c = 1$, MeOH)}.

Scheme 6



In summary, the first total synthesis of (−)-okilactomycin (**1**) has been achieved. Key features of this synthetic venture include a highly diastereoselective oxy-Cope rearrangement/oxidation sequence to secure the C(1) and C(13) stereocenters, a Petasis−Ferrier union/rearrangement to construct the highly congested 2,6-*cis*-tetrahydropyranone ring, a novel tactic to elaborate the fused bicyclic lactone, and an efficient RCM reaction to generate the 13-membered macrocyclic ring. The longest linear sequence proceeded in 29 steps. Importantly, this synthetic venture not only provides a viable route to this interesting antitumor antibiotic, as well as to potential analogues thereof, but also establishes the absolute stereochemistry of natural (+)-okilactomycin (**1**).

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for key transformations and related new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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