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Stereoselective Synthesis of Dysoxylactam A

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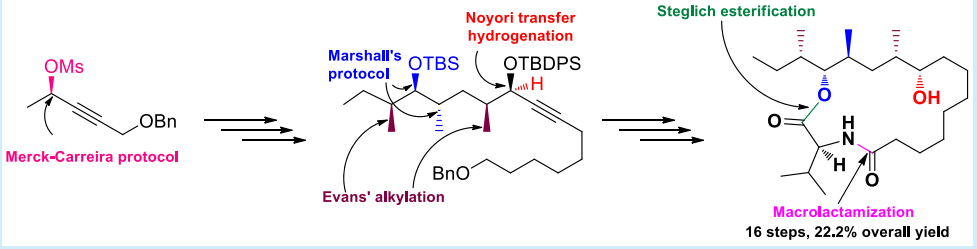
Supporting Information



ABSTRACT: The first report on the stereoselective synthesis of dysoxylactam A is disclosed. The five stereogenic centers of the fatty acid chain are created by utilizing Merck-Carreira and Marshall's propargylation reaction, Evans' alkylation methodology, and Noyori's transfer hydrogenation protocol.

Dysoxylactam A (**1**) (Figure 1) is a 17-membered macrocyclic lipid isolated from the bark of the plant *Dysoxylum hongkongense*.[1] The relative configuration of dysoxylactam was determined by extensive NMR studies, and its absolute configuration was established by X-ray diffraction of the *p*-bromobenzoate derivative. Dysoxylactam A is shown to reverse P-glycoprotein (P-gp) mediated multidrug resistance of chemotherapeutic agents in vitro. It brings about its action through inhibition of the transport function of P-gp protein. It exhibits weak antiproliferative activity against K 562, MCF 7, and KB tumor cell lines. Structurally it is characterized by the presence of the long dihydroxy acid chain possessing five stereogenic centers linked to L-valine via an ester and amide bond.

Herein, we disclose the first stereoselective synthesis of dysoxylactam A by taking advantage of Merck-Carreira and Marshall's asymmetric propargylation protocol, Evans' methodology, and Noyori's transfer hydrogenation protocol. The retrosynthetic disconnection is depicted in Scheme 1. The target was envisioned to be obtained by esterification followed by amide bond formation between compound **3** and Boc-Val-OH (**2**) and subsequent removal of the C9 hydroxy protecting group. The triol derivative **3** might be obtained from 7-octyn-1-ol derivative **4** and Weinreb amide **5** followed by

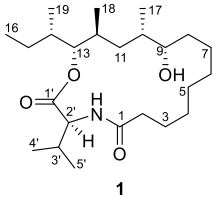


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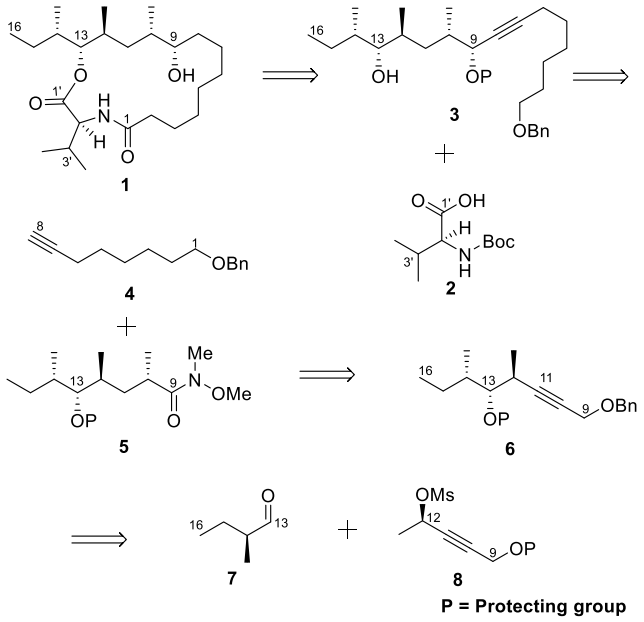
Figure 1. Dysoxylactam A isolated from *Dysoxylum hongkongense*.

Scheme 1. Retrosynthetic Disconnection of Dysoxylactam A



stereoselective hydrogenation. Compound **5** was surmised to be obtained from propargylic ether **6** utilizing Evans' methodology to introduce the C10 stereocenter. We proposed synthesis of alkyne **6** from aldehyde **7** and mesylate **8** following Marshall's protocol.

The synthesis of mesylate **8**, Scheme 2, began by subjecting acetaldehyde **9** to the Merck-Carreira propargylation protocol[2]

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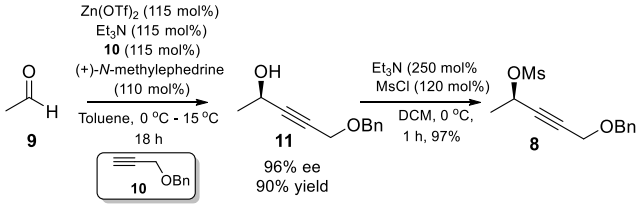
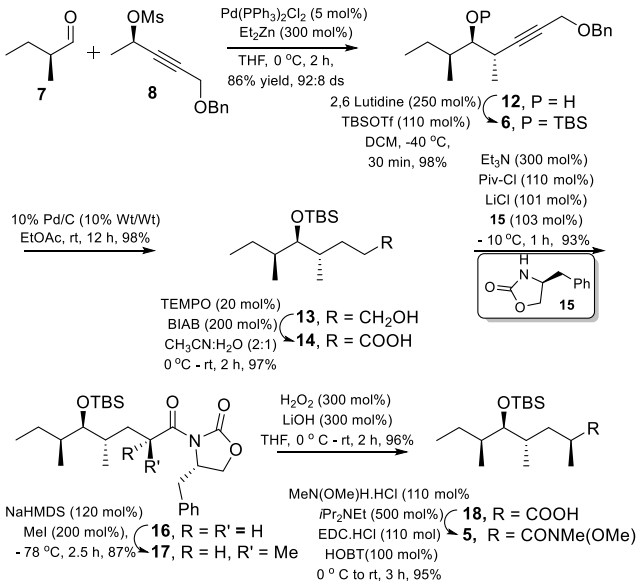
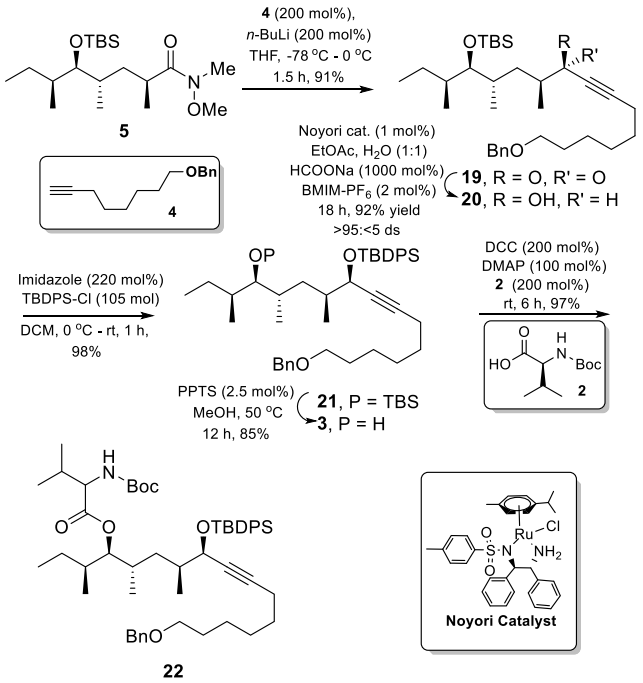
Scheme 2. Synthesis of Mesylate 8



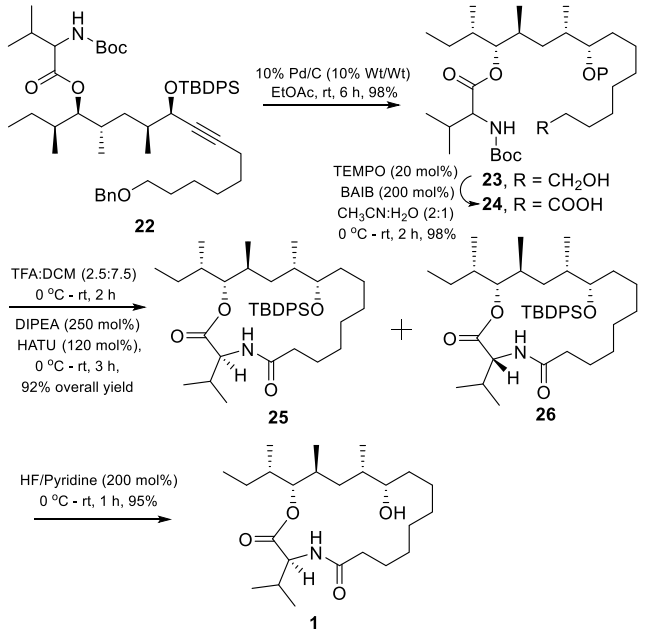
Scheme 3. Synthesis of Weinreb Amide 5



Scheme 4. Synthesis of C1−C16 Subunit 26



Scheme 5. Synthesis of Dysoxylactam A



using benzyl ether **10** to furnish alcohol **11** in 90% yield (96% ee).[3] Mesylation following the standard procedure yielded mesylate **8**. Aldehyde **7** was obtained following a reported procedure using Evans' methodology.[4]

The aldehyde **7** was subjected to Marshall's propargylation[5] with mesylate **8** to furnish homopropargylic alcohol **12** in 86% yield (92:8 ds)[6] Scheme 3. The hydroxyl was protected as its TBS ether **6** under standard conditions. Reduction over Pd/C under an atmosphere of hydrogen yielded the alcohol **13** which upon oxidation using TEMPO and hypervalent iodine reagent[7] afforded the acid **14**. Imide **16** was obtained[8] via reaction of the mixed anhydride, derived from acid **14** and pivaloyl chloride, with oxazolidinone **15**. Methylation using NaHMDS proceeded diastereoselectively to furnish compound **17** which on hydrolysis afforded the acid **18**. Weinreb amide formation proceeded without incident to afford compound **5**.

Lithium acetylide derived from alkyne **4** on reaction with Weinreb amide **5** cleanly afforded the propargylic ketone **19**, Scheme 4. Transfer hydrogenation using (*R*,*R*)-TSDPEN-[RuCl(cymene)] in aqueous media[9] afforded propargylic alcohol **20**[10] in 92% yield (>95% ds). Protection of hydroxy group as its TBDPS ether under standard conditions furnished compound **21**. The stage was now set for coupling the fatty acid derivative with the L-valine derivative. Toward this end, the C13 hydroxy was selectively deprotected by removal of the TBS ether using PPTS in methanol to afford alcohol **3**. Attempted esterification of compound **3** with Boc-Val-OH proved nontrivial, with no product being obtained using DCC, HOBT[11]/EDCI, HOBT[12]/HATU, Hunig's base[13]/BOP-Cl, Hunig's base[14] and cyanuric chloride, and Hunig's base.[15] The reaction proceeded with DCC in the presence of an equivalent amount of DMAP[16] to afford an epimeric mixture of ester **22** that could not be separated, Scheme 4. The diasteroselectively could not be ascertained by examination of ^{1}H NMR spectrum of the ester **22** due to the presence of rotamers. Attempted coupling of alcohol **3** with Fmoc-Val-Cl in the absence[17] or in the presence of 20 mol % of DMAP[18] failed to afford any ester even when run at 60 °C overnight.

Going forward, reduction of the epimeric mixture of ester **22** under hydrogen atmosphere furnished the saturated alcohol **23** as an inseparable mixture, which on oxidation using TEMPO and $PhI(OAc)_2$ yielded acid **24**. Deprotection of the carbamate using TFA furnished the trifluoroacetate salt which on

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treatment with HATU and Hunig's base afforded a separable mixture of lipopeptide **25** and **26** in a 7:3 ratio. Deprotection of C10 hydroxy in compound **25** by removal of TBDPS ether using HF/pyridine[19] yielded target **1** in 95% yield with physical characteristics in excellent agreement with the reported data (Scheme 5).

In conclusion, the first synthesis of macrocyclic lipid dysoxylactam **1** is disclosed. The C9 carbinol stereocenter was created using Noyori's transfer hydrogenation and the C12 and C13 stereocenters using Marshall's propargylation protocol. The C10 and C14 methyl groups were introduced using Evans' protocol. Esterification of C13 hydroxy with Boc-Val-OH proceeded in the presence of an equivalent amount of DMAP to furnish the ester and its epimer. The total synthesis was accomplished in 16 steps with an overall yield of 22.2%.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04426.

Experimental procedures; ^{1}H and ^{13}C NMR spectroscopic characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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