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Total Synthesis of Dysoxylactam A

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Cite This: *Org. Lett.* 2020, 22, 1776−1779 Read Online

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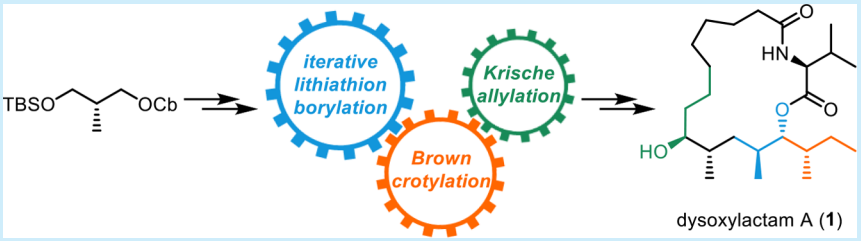


ABSTRACT: The total synthesis of a potent multi-drug-resistant reverser, dysoxylacatam A (**1**), was achieved in a highly efficient and stereocontrolled fashion. The highlights of the strategy enlisted an iterative combination of lithiation−borylation tactics including Aggarwal homologation and Matteson homologation, Brown crotylation, Krische allylation, and ring-closing metathesis to forge the macrocycle.

The phenomenon of multidrug resistance (MDR) is recognized as one of the major obstacles to successful cancer chemotherapy.[1] Cancer drugs often fail to kill tumor cells long-term because of the overexpression of phosphoglycoprotein (Pgp), an efflux pump that transports many of the major drugs out of the cell. One strategy to overcome this problem is the coadministration of agents that can contravene Pgp-mediated multidrug resistance and hence increase intracellular drug concentration, which may have extensive and effective applications in chemotherapy.[2,3] A highly potent MDR inhibitor or reverser with less toxicity is still in great demand.[2] Very recently, Yue and coworkers disclosed their isolation of a novel macrocyclic lipid, dysoxylactam A (**1**) (Figure 1), from the bark of a Chinese plant named *Dysoxylum*

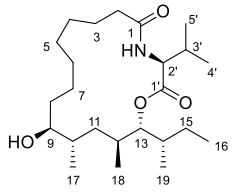


Figure 1. Structure of dysoxylactam A (**1**)

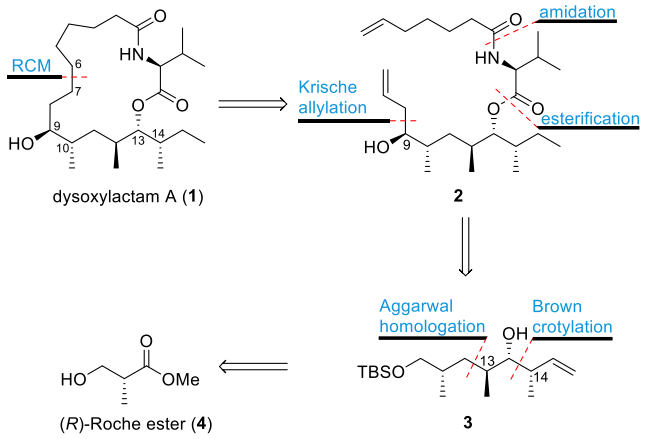
hongkongense.[4] The unprecedented structure was elucidated by means of a combination of nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS) spectroscopic techniques. The relative stereochemical relationship of the five stereogenic centers embedded within the C(9)−C(14) chain was assigned by extensive residual dipolar coupling (RDC)-based NMR studies,[5] and the absolute configuration of dysoxylactam A was established via an X-ray crystallographic study of its *p*-bromobenzoate derivative. Preliminary biological assays indicated that dysoxylactam A can reverse MDR in cancer cells with 28.4−1039.7-fold reversals without noticeable cytotoxicity at 10 μM. Specifically, drug-resistant K562/ADR, MCF7/ADR, and KBV200 significantly restored sensitivities to adriamycin, vincristine, and paclitaxel. P-gp is significantly inhibited by dysoxylactam A, which provides exciting opportunities for tackling MDR in cancer chemotherapy. The unique biological and structural features of dyxoxylactam A are in good accordance with our continuing interest in natural-product-oriented explorations.[6] Herein we describe a concise and stereocontrolled total synthesis of dysoxylactam A.[7]

Structurally, dysoxylactam A consists of a stereochemically rich macrocycle possessing a dense combination of unusual structural features, including an L-valine and a highly functionalized polyketide fragment with an amide linkage between the carboxyl group of the polyketide moiety and the amino group of the L-valine residue. As outlined in our retrosynthetic analysis (Scheme 1), dysoxylactam A (**1**) might be prepared by a ruthenium-catalyzed ring-closing metathesis (RCM) of the bis-olefin **2** and a subsequent palladium-catalyzed alkene hydrogenation. The diastereoselective construction of the homoallylic alcohol in **2** could be secured by Ir-mediated Krische allylation. Dissecting the amide and ester bonds in **2** could further reduce the molecular complexity and result in the polyketide fragment **3**. Taking advantage of

Received: January 7, 2020
Published: February 12, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00074
Org. Lett. 2020, 22, 1776−1779

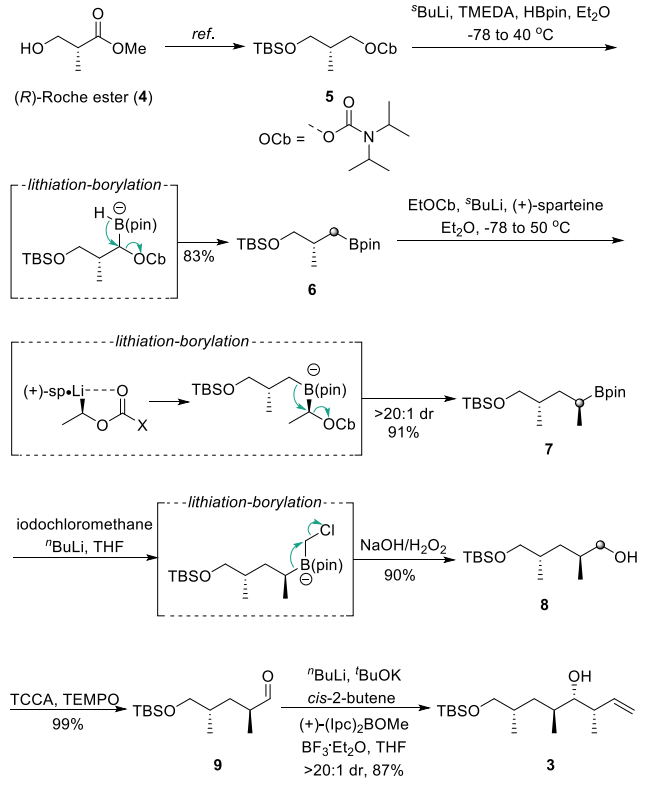
Scheme 1. Retrosynthetic Analysis of Dysoxylactam A (1)



Aggarwal's lithiation−borylation for rapid C−C bond assembly, in combination with Brown crotylation to forge C-13 and C-14 stereogenic centers, monosilylated diol **3** was envisaged to arise from commercially available (*R*)-Roche ester (**4**).

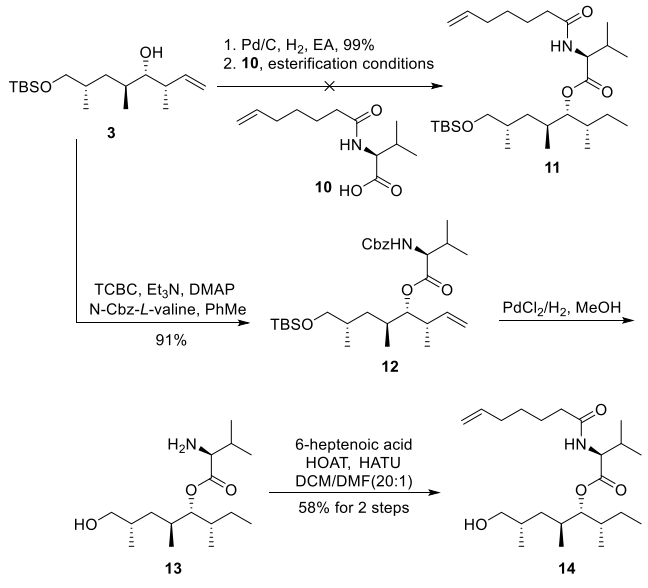
The synthesis of key intermediate **3** began with the conversion of the commercially available (*R*)-Roche ester to carbamate **5** following the known procedures (Scheme 2).[8]

Scheme 2. Synthesis of Homoallylic Alcohol 3



The Hoppe-type carbamate[9] **5** was subjected to *sec*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) to afford a lithiated intermediate, which was then trapped by pinacolborane to give rise to the primary pinacol boronic ester **6** in 83% yield.[10] Subsequently, the asymmetric deprotonation of *O*-ethyl-*N*,*N*-diisopropylcarbamate with *s*-BuLi and (+)-sparteine led to the formation of an enantioenriched lithiated carbamate; then, the addition of the boronic ester **6** triggered a boron−lithium exchange of the resulting sparteine-ligated organolithium species. Both steps were kept at −78 °C to maintain the chemical and configurational stability of the intermediate carbenoid. Then, the temperature was elevated to 50 °C to set in motion the stereospecific 1,2-metalate rearrangement and gave rise to the homologate organoboron **7** with high stereochemical fidelity, providing the secondary boronic ester in 91% yield with excellent diastereoselectivity.[11] (Chloromethyl)lithium, generated by the exposure of iodochloromethane to *n*-butyllithium at −78 °C, was next added to boronate **7** to trigger a Matteson homologation process.[12] The resulting homologate organoboron was *in situ* treated with $NaOH/H_2O_2$ to furnish the primary alcohol **8** in 90% yield. Upon the treatment of alcohol **8** with TCCA/TEMPO,[13] aldehyde **9** was obtained in essentially quantitative yield. Aldehyde **9** further reacted with Brown's (*Z*)-crotyldiisopinocampheylborane, prepared from (+)-diisopinocampheyl(methoxy)borane, and yielded the syn homoallylic alcohol **3** in 87% yield with almost no visible trace of the anti stereoisomer (dr >20:1).[14] With homoallylic alcohol **3** in hand, we first attempted to construct the amide and ester bonds in a straightforward manner (Scheme 3). The terminal

Scheme 3. Synthesis of Intermediate 14



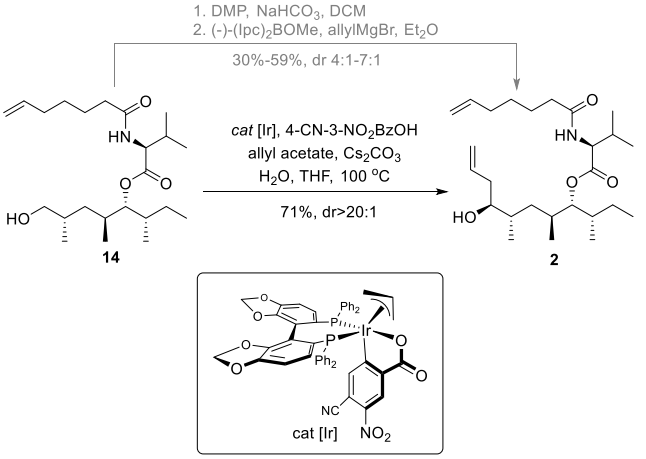
olefin was hydrogenated with Pd/C under 1 atm of hydrogen to afford the corresponding alkane in quantitative yield. However, to condense the resulting alcohol with acid **10** proved unfortunately futile. In the event, the reaction promoted by various coupling agents resulted in low conversions or a detrimental loss of stereo integrity, presumably due to the sterically demanding environment at the secondary hydroxy group. To circumvent the difficult esterification and the concern regarding the possible racemization of the adjacent stereogenic center, we opted to employ a stepwise approach for the further elaboration of **3**. Thus the treatment of *N*-Cbz-L-valine with alcohol **3** under Yamaguchi conditions furnished the congested ester **12** in 91% yield with no detection of appreciable epimerization, as determined by NMR analysis.[15] Ester **12** was subjected to the simultaneous hydrogenation of the alkene and hydrogenolysis of the Cbz protecting group by palladium(II)

https://dx.doi.org/10.1021/acs.orglett.0c00074
Org. Lett. 2020, 22, 1776−1779

chloride in methanol with the concomitant deprotection of the primary silyl ether providing **13**, which was then condensed with 6-heptenoic acid, mediated with HATU/HOAT/DIPEA in DCM/DMF (20:1), to afford amide **14** in 58% yield over two steps.[16]

Amide **14** contains six required stereocenters corresponding to dysoxylacatam A. In this stage, we next investigated the pivotal allylation step. The primary alcohol of **14** was oxidized under Dess–Martin conditions to afford the corresponding aldehyde,[17] which was subsequently submitted to Brown allylation conditions (Scheme 4).[18] The yield and diastereo-

Scheme 4. Synthesis of the Advanced Intermediate 2

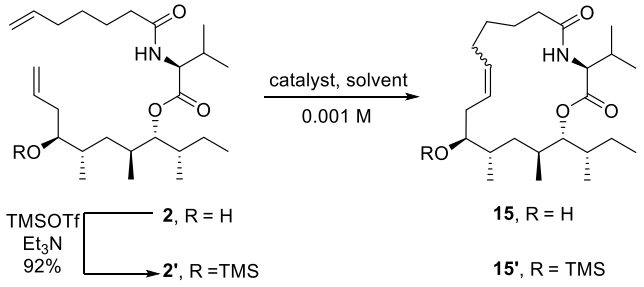


meric ratio of the resulting homoallylic alcohol **2**, however, fluctuated considerably with different batches, which may be attributed to the unrecognized instability of the intermediary aldehyde.[19] To solve this problem, we elected to conduct the transformation using the Krische allylation protocol. An advantage of this allylation approach is that the overall reaction is redox-neutral and avoids a discrete oxidation step, and the catalytic process gradually releases and consumes the deterioration-prone aldehyde as the transformation proceeds.[20] As expected, the iridium-catalyzed carbonyl allylation via transfer hydrogenative coupling gave rise to homoallylic alcohol **2** in 71% yield with remarkable diastereo control.

With the bis-olefin **2** in hand, the stage was set for the key macrocyclization. RCM was first tested on the unmasked olefinic alcohol **2**. In the event, the treatment of diene **2** with 10% second-generation Grubbs–Hoveyda catalyst (HG-II)[21] in toluene or dichloromethane at 40 °C followed by cooling, concentration, and chromatography produced the desired macrocycle **15** in low yield (13 and 22%, respectively) (Table 1). When performing the reaction in dichloromethane at 40 °C, using the second-generation Grubbs catalyst (G-II),[22] the yield of **15** was increased to 40%. The low yields were accompanied by a low mass balance. This was possibly caused by interactions between the hydroxy group and the catalyst, which sequestered the ruthenium carbenoid species.[23] We consequently devised a procedure involving transient masking of the homoallylic alcohol in **2** as the corresponding TMS ether (**2′**). This enabled the subsequent RCM mediated by G-II, furnishing macrocycle **15′** in 70% yield as an inseparable mixture (1:1.5 ratio) of *Z*/*E* isomers.

The final hydrogenation proceeded without incident. The internal alkene in **15′** was cleanly hydrogenated with the concomitant removal of the protective silyl group, and

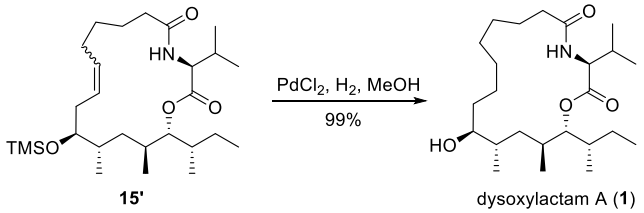
Table 1. Construction of the Macrocycle via Ring-Closing Metathesis



entry	catalyst	solvent	R	*t* (°C)	yield (%)
1	HG-II	PhMe	H	40	13
2	HG-II	DCM	H	40	22
4	G-II	DCM	H	40	40
4	G-II	DCM	TMS	40	70

dysoxylactam A (**1**) was obtained in essentially quantitative yield (Scheme 5). The spectroscopic data (^{1}H and ^{13}C NMR and HRMS) of the synthetic product are in excellent agreement with those reported for the natural product.[3]

Scheme 5. Completion of the Total Synthesis



In summary, the first total synthesis of a highly potent MDR reverser, dysoxylactam A, was accomplished in 15 longest linear steps with 8.8% overall yield from commercially available (*R*)-Roche ester. The synthesis features Aggarwal and Matteson homologations, diastereoselective Brown crotylation, Krische allylation, and an efficient cross-metathesis of functionalized substrates. The present synthesis paves the way for the efficient preparation of analogues for drug development efforts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00074.

Experimental details and data (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c00074
Org. Lett. 2020, 22, 1776−1779

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (21772009 and 21901013), the Shenzhen Peacock Plan (KQTD2015071714043444), the Shenzhen Science and Technology Innovation Commission (JCYJ20170818090017617 and JCYJ20170818090238288), and the GDNSF (2014B030301003).

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Org. Lett. 2020, 22, 1776−1779