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Total Synthesis of Macrocyclic Dysoxylactam A

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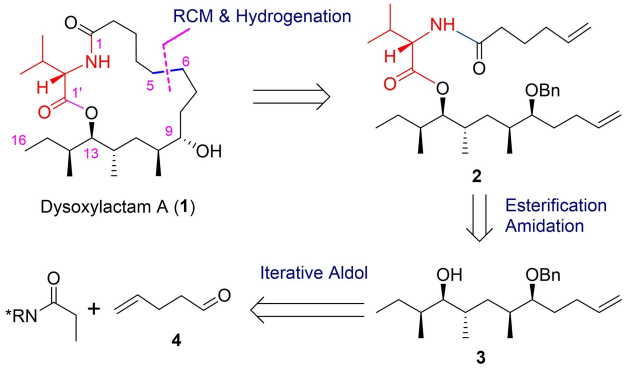
Abstract: The total synthesis of dysoxylactam A, a novel 17-membered macrolactam with potent multi-drug-resistant reversing activities, has been achieved, starting from 4-pentene-1-al in a longest linear sequence of 17 steps and 9.5% overall yield. The key transformations consist of iterative aldol and ring-closing metathesis reactions for the construction of the stereochemically enriched polypropionate scaffold and the macrocycle, respectively.

A persistent effort has been given to the chemical and biological studies of various parts of *Dysoxylum* species, given its folkloric background.[1,2] The leaves of this Chinese herbal plant have been used for treatment of malaria and the twigs for production of Hangkonoides[2] which are used as an anticancer agent.[3] In 2019, Yue and coworkers isolated a novel macrolactam, namely dysoxylactam A (**1**, Scheme 1), from the bark of *Dysoxylum hongkongense*.[4] Significantly, dysoxylactam A, comprising a stereochemically enriched fatty acid skeleton and a valine residue, represents the first example of a 17-membered cyclolipolactam. Moreover, this molecule has been shown to be able to reverse multidrug resistance in cancer cells with the fold-reversals ranging from 28.4 to 1039.7 at a non-cytotoxic concentration of 10 μM. Further studies revealed that it could inhibit the function of P-glycoprotein, a key mediator in the multidrug resistance. The chemical architecture of dysoxylactam A was assigned based on residual dipolar coupling (RDC)-based NMR analysis and validated by X-ray diffraction analysis of its 9-*O*-*p*-bromobenzoate derivative.[4]

The highly promising bioactivity and novel chemical structure of dysoxylactam A have attracted attention from synthetic and medicinal chemists. The first report on the total synthesis of dysoxylactam A was published recently by Chandankar and Raghavan.[5] The synthesis employed Merck-Carreira and Marshall's propargylation, Evans' alkylation, and Noyori's transfer hydrogenation protocols to create the stereocenters presenting in the fatty acid chain, and utilized Steglich esterification and HATU mediated macrolactamization to elaborate the macrocycle. Shortly, Ye et al. disclosed an alternative approach to the synthesis of dysoxylactam A.[6] Their synthesis took advantage of Aggarwal and Matteson homologations, diastereoselective Brown crotylation, and Krische allylation to build up the stereochemically enriched fatty acid fragment and a cross-metathesis reaction (at C6-C7) to construct the macrocycle. Independently and in line with our long interest in macrocyclic natural products,[7] we completed a total synthesis of dysoxylactam A, and herein we report our synthetic approach.



Scheme 1. Dysoxylactam A (**1**) and its retrosynthetic analysis.

Given the polypropionate pattern of the stereochemically crowded region in dysoxylactam A (**1**), we envisioned a straightforward synthetic approach capitalizing mainly on aldol reactions, which has been reliably applied in the synthesis of polyketide natural products, such as deoxyerythronolide B and (−)-pironetin.[8] Thus, the cyclic target compound **1** could be accessible by a Ru-mediated ring-closing metathesis of the linear diene **2** followed by saturation of the resulting double bond (at C5–C6) (Scheme 1). The preparation of diene **2** would involve esterification of the functionalized alcohol **3** with *N*-Boc-valine followed by amide formation with 5-hexenoic acid. The polypropionate fragment **3**, a major focus of the synthesis, could be synthesized in a stereocontrolled manner by using sequential Evans aldol reactions starting from commercially available 4-pentene-1-al (**4**).

Thus, the aldol reaction of 4-pentene-1-al (**4**) with the Evans propionate **5**[9] mediated by dibutylboron triflate led to the known aldol adduct **6**[10] in 89% yield as a single diastereomer, thus establishing the required stereocenter at C9 and C10 (Scheme 2). Reductive removal of the auxiliary under Soai's

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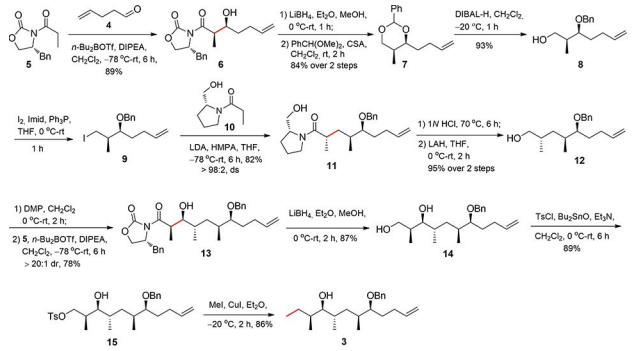


Scheme 2. Synthesis of polypropionate fragment **3**.

conditions[11] ($LiBH_4$, Et_2O/MeOH) furnished the corresponding 1,3-diol, which was subsequently protected with benzaldehyde acetal to give acetal **7** in 84% yield over two steps; the diastereoisomer was not detected with ^1H NMR analysis. Regioselective cleavage of the benzylidene acetal at the less hindered oxygen with DIBAL-*H* afforded primary alcohol **8** in 93% yield.[12] Treatment of the resultant alcohol with I_2 in the presence of imidazole and Ph_3P led to the desired iodoalkane **9**, which was found instable and thus was used immediately for the subsequent alkylation reaction.

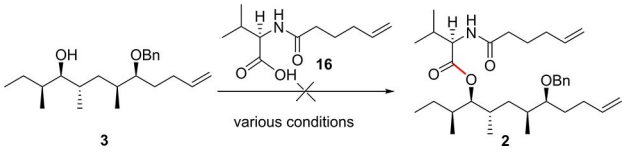
Our next task was to generate the C12-methyl stereocenter which was anti to the C10-methyl group. Fortunately, Evans et al. have developed an effective protocol to geneate such alkyl stereocenters using chiral amide enolates derived from prolinol derivatives.[13] Hence, iodoalkane **9** was allowed to react with a lithium enonlate generated from *D*-prolinol *N*-propionamide **10** by using LDA, furnishing dimethyl amide **11** in 82% yield; the corresponding diastereoisomer was not detected with ^1H NMR analysis. Amide **11** was subjected to hydrolysis with 1 *N* HCl to yield the corresponding acid, which was then allowed to react with lithium aluminumhydride to give primary alcohol **12** (95% over two steps). The resutling primary alcohol was oxidized under Dess – Martin periodinane[14] conditions to give the corresponding aldehyde, which was used in the next aldol reaction without further purification.

Indeed, applying Evans' syn aldol reaction conditions used for the previous addition of **5** and **4**, the reaction of the newly prepared aldehyde and **5** in the presence of dibutylboron triflate afforded the desired adduct **13** in $>20:1$ d.r. and 78% yield. Reductive cleavage of the oxazolidinone in amide **13** with lithium borohydride (Soai's conditions) gave 1,3-diol **14** in 87% yield. Regioselecetive tosylation of the primary hydroxyl group was achieved with TsCl in the presence of Bu_2SnO and Et_3N, leading to tosylate **15**. Treatment of **15** with an excess amount of methyllithium in the presence of CuI provided the required polyketide fragment **3** in 76% yield over two steps.[15]

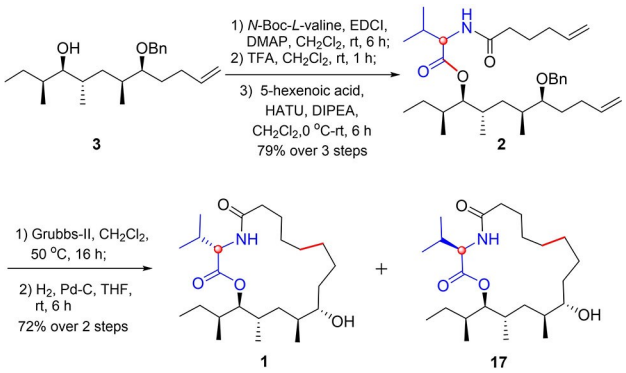
Having the key fragment (**3**) in hand, we set out to couple alcohol **3** with acid fragment **16**, which was easily prepared in two steps from L–Val-OMe.[16] Surprisingly, under various esterification conditions, including with such classical condensation reagents as DCC/DMAP,[17] EDCI/HOBT/DMAP,[18] BOPCl,[19] TCBA/Et_3N/DMAP,[20] and MNBA,[21] the reaction of alcohol **3** with acid **16** did not take place at all to provide the desired ester **2** (Scheme 3).

Alternatively, we tried the esterification of **3** with *N*-Boc-L-valine instead of amide acid **16** (Scheme 4). Indeed, the condesation of **3** and *N*-Boc-L-valine proceeded smoothly in presence of EDCI and an excess amount of DMAP (5 eq.) in CH_2Cl_2.[22] However, epimerization at the valine residue took place simultaneously, resulting in an inseparable epimeric mixture of the esters. Attampts to avoid the epimerization under various conditions were not successul. In addition, it was also found difficult to calculate the exact ratio of the two diastereomers due to rotameric nature of the amino acid derivatives.[23] To move forward, the Boc-protected esters were treated with TFA in dichloromethane to give the free amines as their TFA salts, which were then allowed to react with 5-hexenoic acid in the presence of HATU and Hunig's base[24] to furnish the desired bis-olefin amides **2** in 79% yield (3 steps). The two epimers were still inseparable.

Nevertheless, the final stage was set for the total synthesis, *i.e.*, ring closing metathesis and hydrogenation to complete the macrolactam. Thus, the epimeric mixture of dienes **2** was treated with 20 mole% of grubbs 2nd generation catalyst[25,26] in refluxing dichlomethane; the macrocycles were formed as a inseparable diastereomeric mixture. As the geometry of the newly formed double bond at C5-C6 was of no consequence for the total synthesis of dysoxylactam A (**1**), the resulting macrocyclic olefins were used for the next step without further purification and analysis. In fact, these two steps were carried out in one pot. Subjection of the olefins to hydrogenation in the presence of Pd/C under 1 atm H_2 led to the separable natural product dysoxylactam A (**1**) along with its C-2' epimer **17** in a 3:2 ratio. The spectral and analytical data of the synthetic **1** were in full agreement with those previously reported for the natural and synthetic dysoxylactam A (**1**).[27]



Scheme 3. Attempted esterification of **3** for the synthesis of ester **2**.



Scheme 4. Syntheis of dysoxylactam A (**1**) and its epimer (**17**).

In summary, we have developed an efficient approach to the total synthesis of dysoxylactam A (**1**), in that a longest linear sequence of 17 steps with 9.5% overall yield is registered. The synthesis takes advantage of the iterative Evans aldol reaction sequence to construct the stereochemically crowded polypropionate skeleton and the ring-closing metathesis reaction to elaborate the macrocycle. Application of the present approach to the synthesis of dysoxylactam A derivatives and structure-activity-relationship studies on this novel type of 17-membered macrolactam with multi-drug-resistant reversing activities are currently underway and the results will be reported in due course.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Dysoxylactam A · macrocyclolipopeptide · multi-drug-resistant agent · Aldol reaction · ring-closing metathesis

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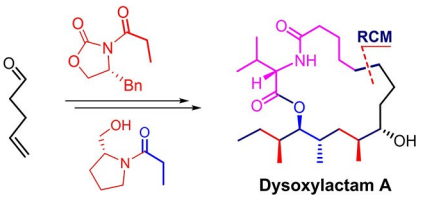

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