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Synthesis of Dysoxylactam A Using Iterative Homologation of Boronic Esters

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Abstract: Dysoxylactam A is a 17-membered macrocyclic lipid which has been found to dramatically reverse multi-drug resistance in cancer cells. Three previous syntheses have been reported in 15–17 steps. Using iterative lithiation-borylation reactions as the key C–C bond forming and stereocontrolling steps, we now describe an 11-step synthesis of dysoxylactam A. The complete sequence only required a total of five chromatographic purifications and used minimal protecting groups making it both rapid and efficient.

Many natural products, particularly those from the family of polyketides, have been shown to have biological properties relevant to human health. For example, dysoxylactam A, a 17 membered macrolipopeptide isolated from the plants of the *Dysoxylum Hongkongense*[1] was shown to reverse the resistance of cancer cells to chemotherapeutic agents by up to 1000-fold at the non-cytotoxic concentration of 10 μM. Thus, the use of dysoxylactam in tandem with anticancer drugs could provide a novel strategy to treat multidrug resistance in cancer cells.

Such was the interest in this natural product, that even though it was only reported in 2019, three total syntheses of dysoxylactam have already appeared (Figure 1). Chandankar completed the first synthesis in 16 steps[2] using a combination of Carreira and Marshall propargylation reactions, Evans alkylation methodology and Noyori transfer hydrogenation to control the stereochemistry present in the fatty acid chain. The macrocycle was formed via a macrolactamisation. Ye's synthesis[3] comprised 15 steps installing the stereochemistry using an Aggarwal homologation and Brown and Krische allylations, with the macrocycle being constructed using a ring-closing metathesis. The third synthesis of dysoxylactam A was reported by Yu in 17 steps[4], using diastereoselective aldol and alkylation chemistry utilising Evans-type auxiliaries, with the macrocycle being constructed again by ring-closing metathesis.

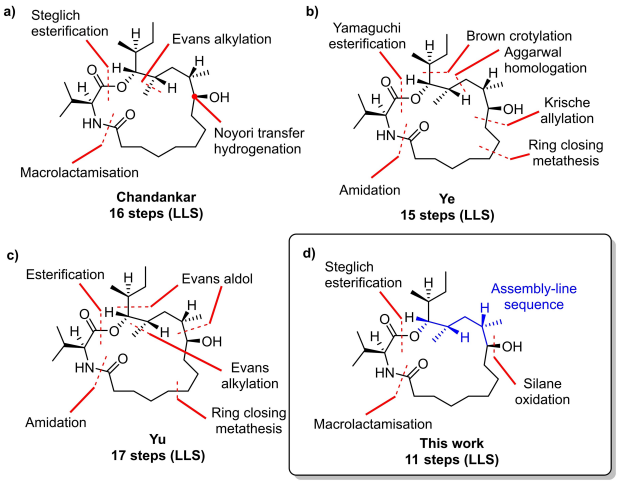
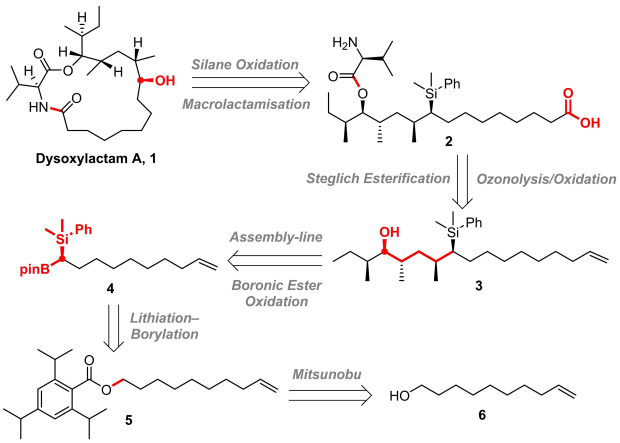


Figure 1. *a–c) Key disconnections employed in previous syntheses of dysoxylactam A. d) This work: an assembly-line approach to dysoxylactam A.*

Herein, we report an alternative strategy to the synthesis of dysoxylactam A which exploits the power of assembly-line synthesis, that is the iterative carbon chain elongation with precise stereocontrol, to construct four of the six stereocentres of the natural product with the other two stereocentres derived from chiral pool molecules. This, in combination with minimal use of protecting groups or functional group interconversions gives dysoxylactam A in fewer steps than previous efforts.

Our retrosynthetic analysis for dysoxylactam A is shown in Scheme 1. We envisaged that the alcohol present in the final product could be derived from the corresponding dimethylphenyl silane, and that the 17 membered macrolactone core



Scheme 1. Retrosynthetic analysis of dysoxylactam A.

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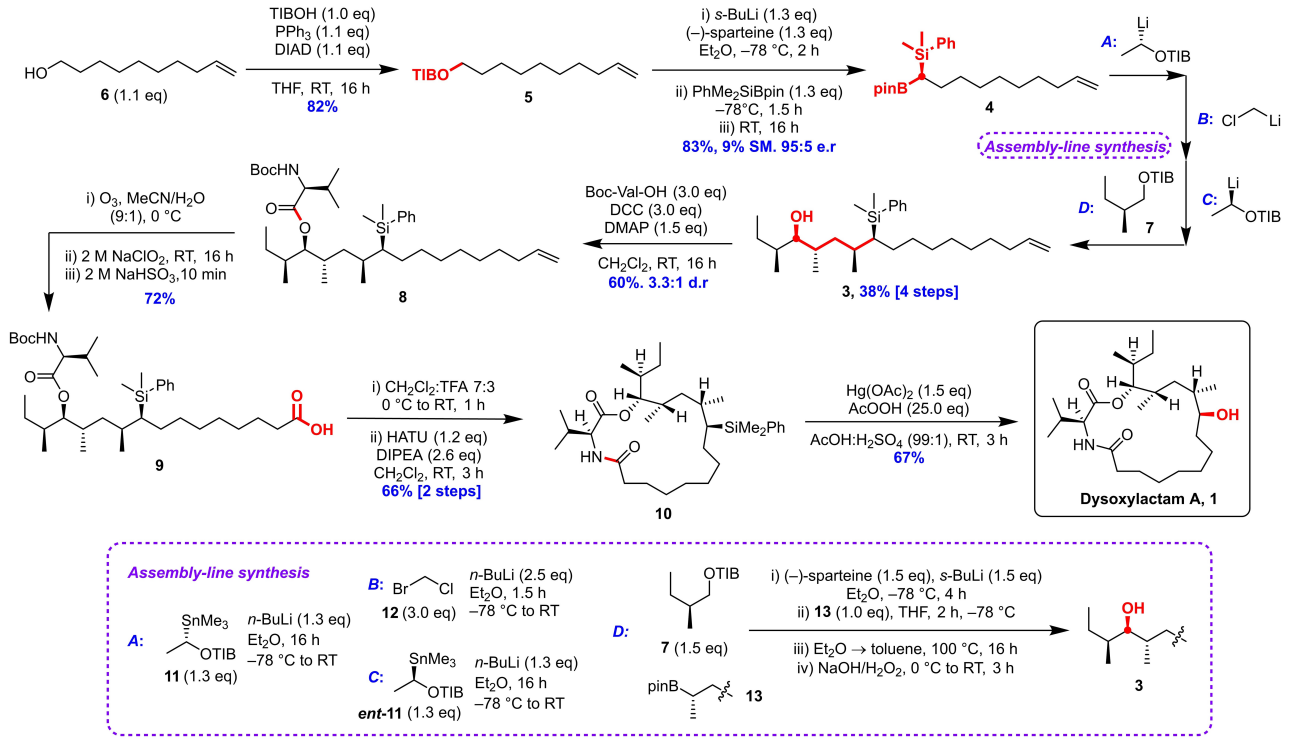


Scheme 2. Assembly-line synthesis of the alcohol intermediate **3** and completion of the synthesis of dysoxylactam.

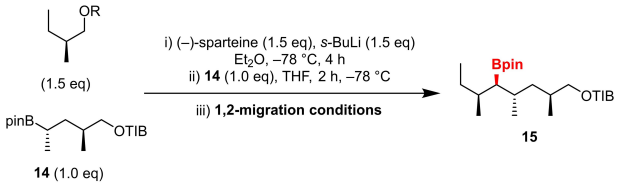
could be formed via a macrolactamisation of the corresponding amino acid **2**.

Masking the carboxylic acid as an alkene leads to the unsaturated alcohol **3**. The alcohol **3** could be generated rapidly from the α-silylboronic ester **4** via a four-step assembly-line synthesis, consisting of four lithiation–borylation reactions followed by oxidation of the boronic ester to the alcohol. Lithiation–borylation could also be employed to synthesize the α-silylboronic ester **4** from the corresponding triisopropylbenzoate ester **5**, which could be derived from the commercially available alcohol **6**.

We began our synthesis from the commercially available alcohol, performing a Mitsunobu reaction to give the corresponding triisopropylbenzoate (TIB) ester **5** (Scheme 2). Lithiation–borylation with Suginome's reagent[5,6] gave the product α-silylboronic ester **4** in 83% yield and 95:5 e.r, with a small amount of the unreacted starting material remaining. These two compounds were inseparable by column chromatography, and efforts to fully consume the starting material entirely by increasing the equivalents of base, (−)-sparteine and boronic ester proved unsuccessful. This issue was inconsequential however, as the unreacted starting material could be carried through the assembly line as a non-reactive species – in fact, this lithiation–borylation proceeded cleanly and a simple silica gel filtration was enough to prepare the boronic ester for the following assembly-line synthesis. (−)-Sparteine could be re-isolated in >90% yield through an acid-base wash.[7] Treatment of boronic ester **4** with (*S*)-Li TIB ester derived from **11**,[7] followed by a Matteson reaction with chloromethyl lithium[8,9] and then reaction with (*R*)-Li TIB ester derived from ***ent*-11**, and finally the lithiated TIB ester **7** with an oxidative workup gave the product alcohol **3** in 38% yield over the four steps without intermediate purification and with complete stereocontrol.

The final lithiation–borylation step initially proved problematic and so was examined on a similarly hindered model boronic ester **14**. Under standard conditions for the 1,2-migration (RT, Et_2O, 16 h) we only obtained the boronic ester product in 18% yield with a 2:1 ratio of C-migration to O-migration, (Table 1, Entry 1). Some boronate complex also remained. Unfortunately, the use of $MgBr_2$ in MeOH[10,11] (Entry 2) resulted in even more O-migration. We have previously observed competing O migration in the coupling of two hindered coupling partners since they generate a highly congested ate-complex.[12] In that study we found that using

Table 1. Optimisation of the 1,2-metallate rearrangement.



Entry	R	Conditions	C:O migration ratio	Isolated Yield
1	TIB	RT, 16 h	2:1	18%
2	TIB	$MgBr_2$ (1 M in MeOH)	1:1	16%
3	Cb	$MgBr_2$ (1 M in MeOH)	1:4	N.D.
4	TIB	$Et_2O \rightarrow CHCl_3$, 60 °C	7:1	41%
5	TIB	$Et_2O \rightarrow PhMe$, 100 °C	10:1	63%

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the diisopropylcarbamate (Cb) instead of the TIB ester gave improved C- over O-migration and so this was tested here. Unfortunately, again O-migration competed with C-migration (Entry 3). It was also known that non-polar solvents can promote the desired 1,2-migration by strengthening the complexation between the lithium cation and the TIB ester and so this was tested.[13,14] After lithiation-borylation, we carried out a solvent exchange from Et_2O to $CHCl_3$ followed by heating.

Not only did solvent exchange result in a much-improved yield but it also a greatly improved the ratio of C- to O-migration (Entry 4). Further improvements were observed with solvent exchange to toluene giving a 10:1 ratio of C- to O-migration (Entry 5). In both cases, elevated temperatures during the 1,2-metallate rearrangement consumed all the boronate complex. These conditions were used in the final lithiation-borylation step of the assembly line synthesis.

We believe that the origin of the competing contra-thermodynamic O-migration may be due to the conformation of the boronate complex. In situations where both the boronic ester and the substituent on the TIB ester are hindered, significant steric interactions between the two large groups occur in the conformation required for C-migration (Figure 2). When the two large substituents are placed opposite to each other, relieving steric hindrance, the group that is anti-periplanar to the leaving group is now the oxygen of the pinacol ester which is set up to migrate instead. This explanation could account for the increased O-migration observed with sterically hindered substrates.

With the alcohol **3** in hand, we explored the esterification of the hindered secondary alcohol with *N*-Boc-L-valine. Such esterifications are notoriously difficult,[15] with this step being highlighted as problematic in previous syntheses of dysoxylactam A;[2–4] which was our experience too. Using a modification of Chandankar's DCC/DMAP conditions, we obtained the desired ester **8** in moderate yield, but with a significant amount of epimerisation.[2] The use of HOAt or HOBt did not prevent this epimerisation, but fortunately separation of diastereoisomers was possible. Ozonolysis-oxidation procedure converted the alkene to the corresponding carboxylic acid **9** cleanly and in one-pot.[16] Removal of the Boc group revealed the free amine **2**, which could then be directly subjected to the macrolactamisation conditions using HATU,[17,18] producing the desired macrocycle **10** in 66% yield. The final silane oxidation required some exploration. Using typical Fleming-Tamao conditions

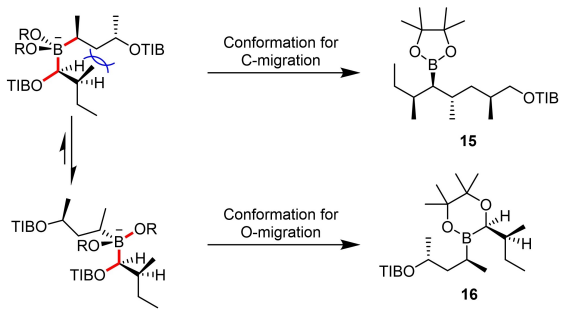

Figure 2. *Conformations required for C-migration and O-migration.*

(HBF_4, *m*-CPBA)[19] and Woerpel's silane oxidation conditions (*t*-BuOOH, KH, TBAF)[20] both resulted in ring opening of the macrocycle. Fleming's one pot procedure[21,22] using KBr/AcOOH resulted in the formation of the ketone as a result of over-oxidation.[23] However, using $Hg(OAc)_2$/AcOOH[21] proceeded smoothly, giving the product dysoxylactam A in a 67% yield. The physical data of the synthetic material completely matched that from the literature (^1H, ^{13}C NMR, $[\alpha]^D$).[1]

In conclusion, we have synthesized the macrolipopeptide dysoxylactam A in 11 steps (longest linear sequence). Our route features an assembly line synthesis which rapidly constructs the stereochemically dense lipophilic portion of the molecule in four steps with only a single chromatographic purification. The complete sequence only required a total of five chromatographic purifications and used minimal protecting groups (a Boc group), making it both rapid and efficient. Indeed, using Hendrickson's measure of percentage ideality[24,25] (the percentage of steps which form skeletal bonds (C–C and C-heteroatom) that end up in the final product out of all total steps in a synthesis), our synthesis achieved a high score of 73%.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Assembly-line · Homologation · Lithiation-Borylation · Macrocyclic Synthesis · Polyketides

[1] C.-P. Liu, C.-Y. Xie, J.-X. Zhao, K.-L. Ji, X.-X. Lei, H. Sun, L.-G. Lou, J.-M. Yue, *J. Am. Chem. Soc.* **2019**, *141*, 6816.
[2] S. S. Chandankar, S. Raghavan, *Org. Lett.* **2020**, *22*, 653–655.
[3] M. Yang, W. Peng, Y. Guo, T. Ye, *Org. Lett.* **2020**, *22*, 1776–1779.
[4] D. Prabhakar Reddy, B. Yu, *Chem. Asian J.* **2020**, *15*, 2467–2469.
[5] M. Suginome, H. Nakamura, Y. Ito, *Angew. Chem. Int. Ed.* **1997**, *36*, 2516–2518; *Angew. Chem.* **1997**, *109*, 2626–2628.
[6] M. Suginome, H. Nakamura, Y. Ito, *Chem. Commun.* **1996**, 2777–2778.
[7] M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183–188.
[8] K. M. Sadhu, D. S. Matteson, *Organometallics* **1985**, *4*, 1687–1689.
[9] D. S. Matteson, B. S. L. Collins, V. K. Aggarwal, E. Ciganek, *Org. React.* **2021**, *105*, 427–860.
[10] V. Bagutski, R. M. French, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 5142–5145; *Angew. Chem.* **2010**, *122*, 5268–5271.
[11] S. Roesner, D. J. Blair, V. K. Aggarwal, *Chem. Sci.* **2015**, *6*, 3718–3723.
[12] A. Millán, P. D. Grigol Martinez, V. K. Aggarwal, *Chem. Eur. J.* **2018**, *24*, 730–735.
[13] S. Roesner, J. M. Casatejada, T. G. Elford, R. P. Sonawane, V. K. Aggarwal, *Org. Lett.* **2011**, *13*, 5740–5743.
[14] A. Varela, L. K. B. Garve, D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2017**, *56*, 2127–2131; *Angew. Chem.* **2017**, *129*, 2159–2163.
[15] M. Tsakos, E. S. Schaffert, L. L. Clement, N. L. Villadsen, T. B. Poulsen, *Nat. Prod. Rep.* **2015**, *32*, 605–632.
[16] B. M. Cochran, *Synlett* **2016**, *27*, 245–248.
[17] S. Wen, G. Packham, A. Ganesan, *J. Org. Chem.* **2008**, *73*, 9353–9361.

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[18] S. Gahalawat, S. K. Pandey, *Org. Biomol. Chem.* **2016**, *14*, 9287–9293.
[19] Y. Matsumoto, T. Hayashi, Y. Ito, *Tetrahedron* **1994**, *50*, 335–346.
[20] J. H. Smitrovich, K. A. Woerpel, *J. Org. Chem.* **1996**, *61*, 6044–6046.
[21] I. Fleming, P. E. J. Sanderson, *Tetrahedron Lett.* **1987**, *28*, 4229–4232.
[22] K. Fukuda, M. Miyashita, K. Tanino, *Tetrahedron Lett.* **2010**, *51*, 4523–4525.
[23] T. Morimoto, M. Hirano, H. Ashiya, H. Egashira, X. Zhuang, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4143–4144.
[24] J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, *97*, 5784–5800.
[25] T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657–4673.

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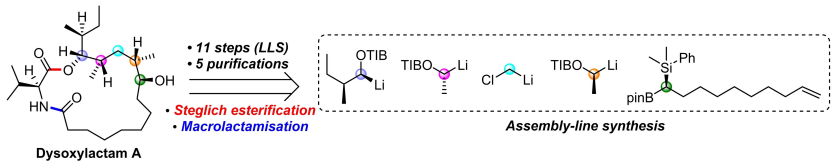

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