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Report

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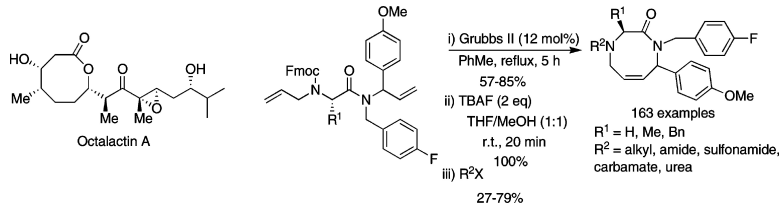

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Design and Synthesis of Medium-Ring Lactam Libraries Inspired by Octalactin A. A Convergent−Divergent Approach

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Small molecule compound libraries based on medium rings[1] are virtually unknown.[2] This critical gap in the literature is probably caused by two main factors. First, medium ring natural products are themselves uncommon and therefore less likely to be the object of total synthesis efforts.[3] Second, there is a widely held view that medium rings remain the most challenging and difficult systems to synthesize.[4] As part of a program to identify interesting chemotypes for library development, we examined several medium-ring natural products. One system in particular, namely, octalactin A (**1**) (Figure 1),[5] continues to attract intense interest because of its fascinating architecture and potent antitumor profile.[6]

The rare, saturated eight-membered lactone core appeared to be an attractive feature on which to base a new library template. Our previous experience with the total synthesis of the octalactins[7] and of other eight-membered lactone natural products[8] by means of a facile direct lactonization from the saturated seco acid ("zip-up" approach) and via an equally efficient ring-closing metathesis to afford oxocenes from the diene ester ("zip-down" approach),[9] provided the enabling technology for this project and prompted us to proceed with this scaffold.

Because it was desirable for us to have the flexibility to introduce additional functionality that could later be easily modified, we settled on a convergent−divergent strategy of constructing lactam rather than lactone libraries via RCM (Scheme 1).

In the convergent phase, three simple, commercially available building blocks served as sources of diversity for the scaffold: protected L-amino acids, benzaldehydes, and benzyl amines. Once the desired frameworks were in hand, diversification at the secondary amine R^2N was carried out in parallel fashion (divergent phase) to afford compound libraries of amines, amides, sulfonamides, carbamates, and ureas.

As a guiding principle for the creation of molecules most likely to have druglike properties, all of the entries were screened in silico prior to synthesis to comport with Lipinski's Rules.[10] We are now pleased to report a 163-member demonstration library, the first based on a monocyclic medium-ring platform. The synthesis of the scaffold began with the commercially available *t*-butyl ester hydrochloride salts of the amino acids glycine, alanine, and phenylalanine (Scheme 2). The salts were allylated by a modified one-pot literature procedure (CH_2=$CHCH_2Br$, $NaHCO_3$, LiI),[11] and then protected with the Fmoc group to afford the *N*-allyl esters **12**−**14** in 53−81% yield. Attempts at unmasking the carboxylic acid using conventional ester hydrolysis protocols proved unsuccessful and resulted in significant racemization with the two chiral amino acids. However, the use of Et_3SiH in TFA/CH_2Cl_2 (1:1)[12] produced the desired acids **15**−**17**.

To maximize the number compounds available for biological screening with a minimum of synthetic effort, we decided to employ a single racemic coupling partner. The secondary allylic amine **5** was easily prepared in 82% yield in one-pot and on a 10 g scale by stirring an equimolar mixture of *p*-methoxybenzaldehyde with *p*-fluorobenzylamine in ether in the presence of magnesium sulfate, followed by $BF_3 \cdot OEt_2$-catalyzed addition of vinyl Grignard.[13]

Amidation was accomplished most effectively via the acyl chloride using a resin-bound triphenylphosphine[14] to give the requisite diene amides **18**−**20** in 64−87% yield. With the amides in hand, the key ring-closing metathesis reaction was attempted. Although we had previously shown that RCM with esters in the octalactin series was facile at 40 °C,[9] presumably because of a reactive conformation induced by the stereogenic centers, it was not clear that a similar bias could overcome the population of unfavorable amide rotamers, which would preclude cyclization.

Indeed, no reaction was observed at room temperature or even at elevated temperatures up to 100 °C. Gratifyingly, heating in refluxing toluene with either the Grubbs' first- or second-generation catalysts for 5 h afforded the desired diastereomeric (or racemic in the case of glycine) lactams **21**−**23** in about a 1:1 ratio. There appeared to be no preference for either diastereomer during the cyclization, and no evidence of double-bond migration was observed.

It was found that the yields were significantly improved by employing a continuous purge of ethylene with nitrogen

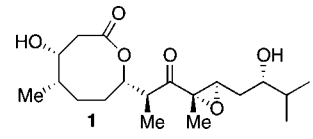

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Figure 1. Octalactin A.

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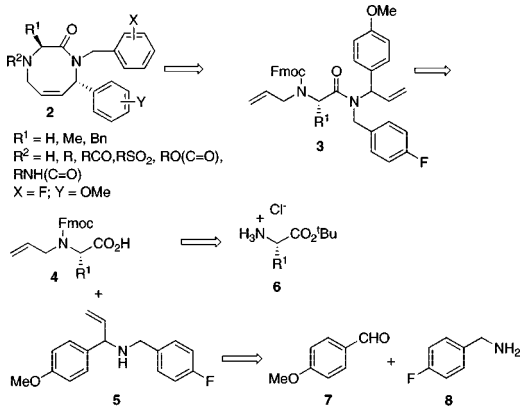
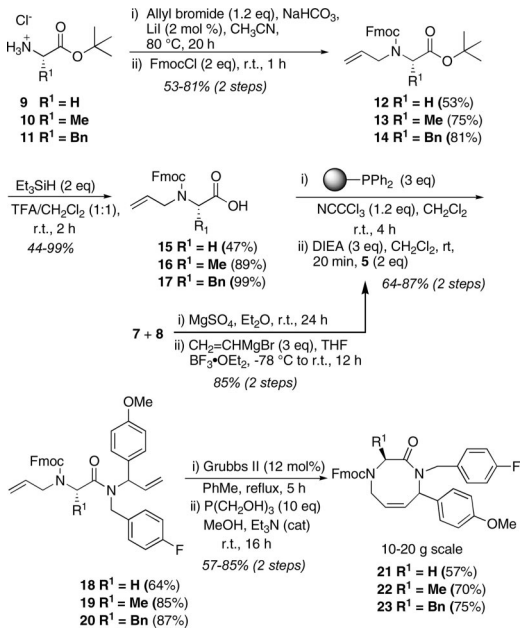
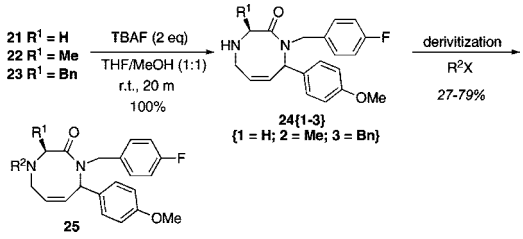
Scheme 1. Retrosynthetic Analysis of the Basic Scaffold



Scheme 2. Scaffold Synthesis via RCM



Scheme 3. Deprotection and Derivatization of the Scaffold

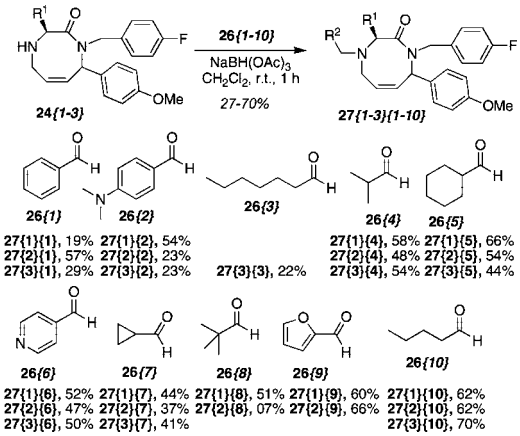


or argon gas and by using $P(CH_2OH)_3$ as a ruthenium scavenger at the end of the reaction.[15] In this manner, the reaction is reliably scalable to 1−2 g in 57−75% yield. Although the Fmoc-protected diastereomers **22** and **23** could be separated via chromatography, this was deemed unnecessary for purposes of biological annotation.

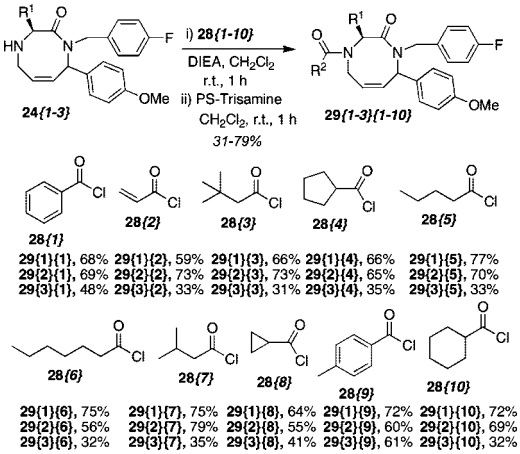
Finally, deprotection of the Fmoc group was carried out with TBAF in THF/MeOH (1:1)[16] to give quantitatively the secondary amines **24**{*1*−*3*} (Scheme 3).

With the key scaffolds available in sufficient supply, derivatization of the amine R^2N was performed. We selected functional groups most likely to be found in pharmacophores, namely, tertiary amines, amides, sulfonamides, carbamates, and ureas (Schemes 4−8). The incorporation of additional

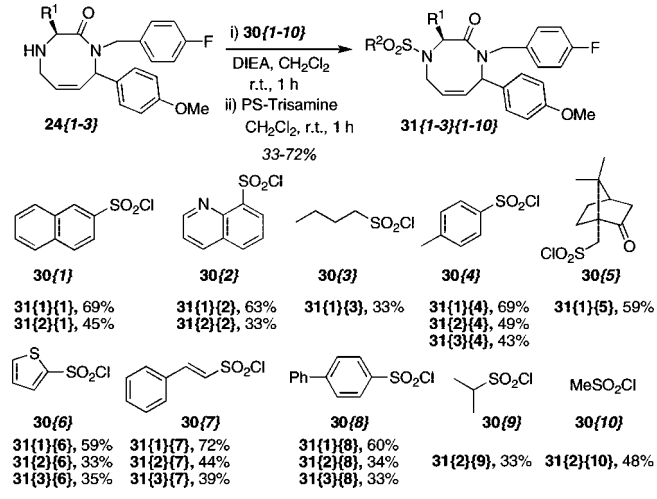
Scheme 4. Tertiary Amine Derivatization



Scheme 5. Amide Derivatization



Scheme 6. Sulfonamide Derivatization

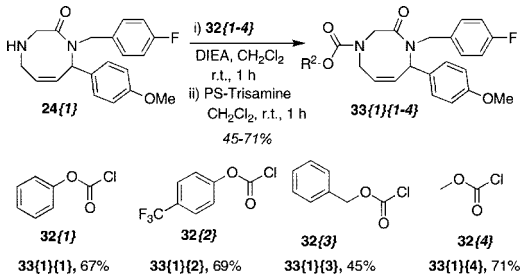


rings, functional groups, and stereocenters in these units further contributed to the diversity of the final structures.

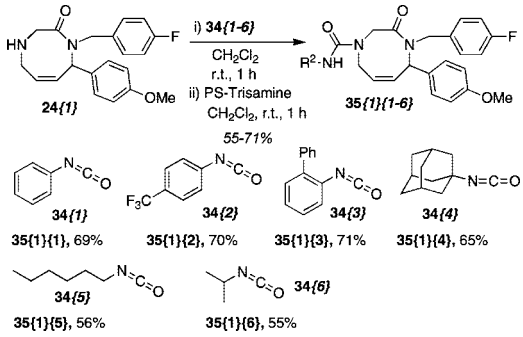
The alanine and phenylalanine scaffolds **21**−**22** were each used after Fmoc deprotection as a mixture of diastereomers for the derivatization studies. In most cases the diastereomeric mixture of cis and trans library members consisting of their respective tertiary amines (Scheme 4), tertiary amides (Scheme 5), and sulfonamides (Scheme 6) were easily separable by short-path flash chromatography.

Resin-bound scavengers (e.g., PS-trisamine)[17] were employed to assist with isolation; however, for characterization

Scheme 7. Carbamate Derivatization



Scheme 8. Urea Derivatization



and annotation purposes, all of the diastereomerically separated (or racemic in the case of the glycine derivatives) compounds were further subjected to chromatography, and their identity and purity confirmed by ^{1}H NMR and high-resolution mass spectrometry. The unoptimized yields for the total library ranged from 7−79%.

Not surprisingly, the yields for the glycine derivatives tended to be higher across the board because of the the less crowded enviroment near the secondary amine. Only the glycine scaffold was used for the carbamate and urea library members in which cases the yields of pure racemic material was uniformly good.

All of the compounds have been submitted to the NIH Molecular Libraries Screening Centers Network (MLSCN) for evaluation with a broad range of assays. In advance of the MLSCN annotation, we elected to subject several randomly selected library members to a preliminary antiproliferative biological screen with murine L1210 lymphocytic leukemia cell lines. The results are summarized in Table 1.

It is significant that these compounds all show very low micromolar to submicromolar inhibition in this assay. Although the antiproliferative activities of this subset do not yet match those of established anticancer drugs such as daunorubicin and mitoxantrone, both of which, under similar experimental conditions, consistently inhibit the growth of various tumor cell lines in the low nanomolar range, they clearly validate the success and relevance of these medium-ring libraries. The selected sulfonamide derivatives from the glycine, alanine, and phenylalanine series all exhibited attractive profiles, and the camphorsulfonamide glycine derivative **31**{*1*}{*5*} showed the best activity of those examined.

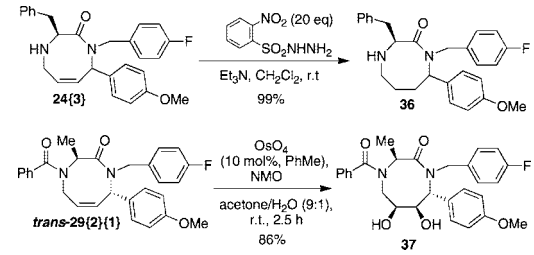
It should also be noted here that the initial in silico validation studies carried out at the KU-CMLD flagged the compound **31**{*3*}{*4*} and its close analogs as occupying

Table 1. Antiproliferative Activity of Novel Eight-Membered Lactams Inspired by Octalactin A in L1210 Tumor Cells In Vitro[a]

entry	compound	L1210 cells (day 4) IC_{50}, μM[b]
1	**21**	1.14 (±0.09)
2	**29**{*3*}{*3*}	1.43 (±0.07)
3	**29**{*3*}{*7*}	1.48 (±0.11)
4	**31**{*1*}{*1*}	1.09 (±0.09)
5	**31**{*1*}{*5*}	0.47 (±0.03)
6	**31**{*2*}{*1*}	2.57 (±0.12)
7	**31**{*2*}{*8*}	1.19 (±0.08)
8	**31**{*2*}{*10*}	1.16 (±0.06)
9	**31**{*3*}{*4*}	1.54 (±0.13)
10	**33**{*1*}{*1*}	0.64 (±0.04)

[a] Concentrations of compound required to inhibit by 50% (IC_{50} values) the metabolic activity of L1210 tumor cells, using MTS:PMS assay at day 4 in vitro. IC_{50} values were calculated from linear regression of the slopes of the log-transformed concentration survival curves. [b] Means ± SD (n = 3).

Scheme 9. Modification of the Lactam Olefin

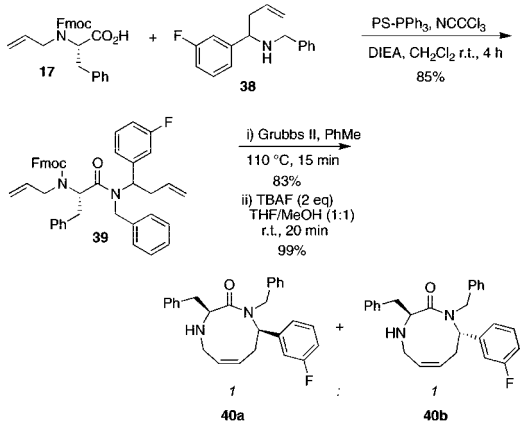


regions of chemical property space that simultaneously had disproportionately strong numbers of bioactive screens against a variety of cancer cell lines and were sparsely populated. Specifically, from chemical diversity space models developed to spatially distinguish clusters of bioactive compounds from predominantly inactive scaffolds,[18] we noted that **31**{*3*}{*4*} and its analogs were found in chemical space regions with active/inactive ratios several standard deviations above the mean for the NCI-H322 M and KM12 cell lines and that the compound densities in these regions were consistently several standard deviations below the norm as represented within the standard NCI screening set. Significantly, there are no close octalactin analogs to these compounds in the entire PubChem Compound Collection, other than those originating from this study.

We have further demonstrated that the olefin **24**{*3*} can be conveniently and quantitatively reduced with diimide[19] to give the conformationally less rigid scaffold **36**. Alternatively, highly stereoselective dihydroxylation of the trans isomer of **29**{*2*}{*1*} for example gave **37** in 86% yield, providing additional functionality (Scheme 9). In this manner, many more library members are potentially within reach with minimum effort.

Finally, we have demonstrated that nine-membered lactams are also readily accessible simply by adding allyl Grignard to the Schiff bases described above. In this case RCM is remarkably facile, giving the Fmoc-protected lactams as a 1:1 mixture of diastereomers in 83% yield in only 15 min (Scheme 10). This observation stands in sharp contrast to an earlier observation made by Guibé regarding the formation of nine-membered lactams by RCM.[20] Deprotection with TBAF followed by chromatographic separation afforded quantitatively **40ab**.

Scheme 10. Facile Synthesis of Nine-Membered Lactam Scaffold



In summary, we have produced the first eight-membered small compound library inspired by the important natural product octalactin A. The scaffolds were prepared in only six steps from inexpensive amino acid esters. The 163-membered collection features a diversity of topology, stereochemistry, and functionality. Other druglike designs based on the eight-membered and other medium-ring platforms are in progress and will be described as developments warrant.

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Supporting Information Available. Detailed experimental procedures and ^{1}H NMR data for a representative number of compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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