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Total Syntheses of Cyclomarin and Metamarin Natural Products

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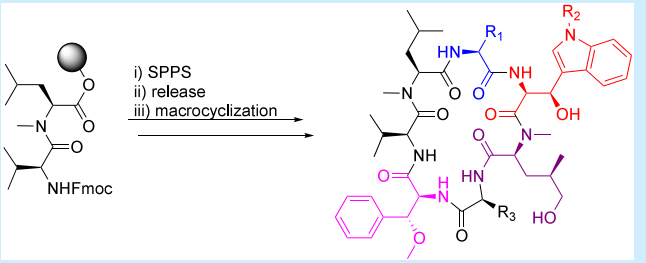
ABSTRACT: The first total synthesis of the heptapeptide Cyclomarin A (CymA) was achieved via new routes to chiral amino acid building blocks (highlighted) and solid-phase peptide synthesis. A structurally misassigned epimer of CymA (CymA′), Cyclomarin C, and Metamarin were also synthesized. Affirmation of the syntheses was corroborated by observations that the synthetic molecules have antimicrobial activities mirroring those of the natural products. Interestingly, CymA′ is more potent than CymA.



Twenty-five years ago, Clardy and co-workers reported the isolation and structure elucidations of three cyclo-heptapeptides collectively called the cyclomarins (Cyclomarin A, B, and C).[1] Their distinguishing features are four amino acids that are derived from stereospecific biosynthetic oxidations of proteinogenic amino acids (*i.e.*, (2*S*,4*R*)-*N*-methyl hydroxyleucine, (2*S*,3*R*)-3,5-dimethyldehydro norleucine, (2*S*,3*R*)-*β*-methoxy phenylalanine, and (2*S*,3*R*)-*β*-hydroxy tryptophan having a *N*-*tert*-prenyl moiety that is epoxidized in the major congener).[2] Interestingly, there are homologous natural products lacking some of the aforementioned amino acids (*i.e.*, Cyclomarin D,[2] Metamarin,[3] and M10709[4]) (Figure 1).

The structural similarities of the peptides belie a strikingly diverse spectrum of biological activities. CymA was initially reported to have excellent *in vitro* and *in vivo* anti-inflammatory properties, as well as modest cytotoxicity (IC_{50} = 2.6 μM) against certain human cancer cell lines.[1] In 2011, Schmitt and co-workers at Novartis described the potent activity of the cyclomarins against *Mycobacterium tuberculosis* (*Mtb*).[5] Their spectrum of biological activities was later expanded to include anti-*Plasmodium* activity.[6] It is highly unusual for natural products to have diverse activities in mammals and antimicrobial activity against bacterial and eukaryotic pathogens.[1,5,6]

The range of biological activities and medicinal potential of this group of cycloheptapeptide natural products warrant in-depth structure–activity relationship studies and the development of methodologies for their efficient chemical syntheses. Moreover, there is an unresolved conflict regarding the absolute configuration of the HyTrp epoxide moiety in CymA. In the original paper, the crystal structure of CymA diacetate clearly shows that the epoxide has an *S*-configured chiral center.[1] However, the rendered structure in the same paper and all subsequent papers show the epoxide having *R* configuration.[1,2,6,7] To validate the structure and clarify the biological activities, we were motivated to synthesize CymA and the reported epimer (denoted as Cyclomarin A′ in Figure 1). The published syntheses have the intrinsic drawbacks of

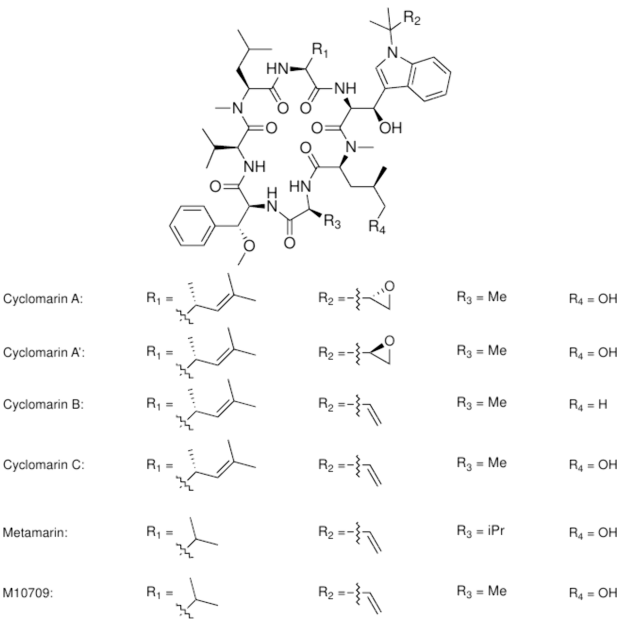


Figure 1. Cyclomarin A–D, Cyclomarin A′, Metamarin, and M10709

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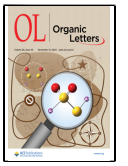
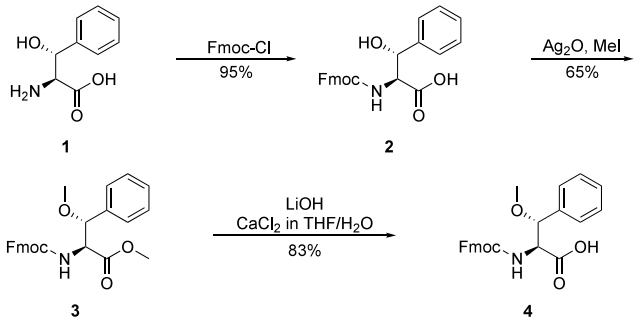


solution-phase synthesis: (i) multistep solution-phase reactions and purifications of amino acid building blocks and intermediates, (ii) challenging late-stage deprotections, and (iii) usage of multiple protecting groups. Herein, we report an efficient synthetic approach for CymA, CymC, and Metamarin using Fmoc solid-phase peptide synthesis (SPPS). The advantages of SPPS are complemented by new and efficient routes for the asymmetric syntheses of the four non-proteinogenic amino acids found in the cyclomarin family members.

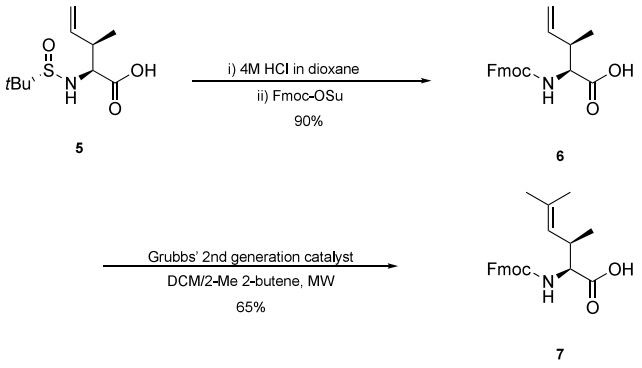
Theoretically, the most direct route for the synthesis of *N*-Fmoc (2*S*,3*R*)-*β*-methoxy phenylalanine (Fmoc-MeOPhe-OH) (**4**) is a two-step sequence of *N*-protection and *O*-methylation of commercially available (2*S*,3*R*)-*β*-hydroxy phenylalanine (**1**).[8] However, base-promoted *O*-methylations of *N*-carbamate protected, *β*-hydroxy amino acids are notoriously prone to side reactions, including *N*-methylation, esterification, oxazolidone formation, *β*-elimination, and retro-aldol.[9] Accordingly, *N*-Boc (2*S*,3*R*)-*β*-methoxy phenylalanine has been synthesized via a *N*-Boc, monosilyl *O*-protected diol (prepared in two steps) that was subsequently subjected to *O*-methylation, desilylation, and oxidation.[7a] Alternatively, the desired amino acid has been prepared in five steps from **1** via an *N*-phthalimido intermediate whose esterification under *O*-methylation conditions necessitates both *N*-protecting group interconversion and ester hydrolysis.[10] In the interest of efficiency, we sought to effect the direct *O*-methylation of Fmoc-(2*S*,3*R*)-*β*-hydroxy phenylalanine (**2**). Though we observed esterification, we were gratified to find that the desired *O*-methylation could be effected using MeI and the mild base Ag_2O in 65% yield without loss of the Fmoc-protecting group or other side reactions. Hydrolysis of ester **3** to the desired Fmoc-MeOPhe-OH (**4**) using the LiOH/$CaCl_2$ protocol[11] occurred with minor racemization (<3%). Subsequent recrystallization of the crude acid afforded **4** in high yield and purity. This route is only three steps from **1** (Scheme 1).

Scheme 1. Synthesis of Fmoc-MeOPhe-OH 4



Trisubstituted *γ*,*δ*-unsaturated *α*-amino acids like (2*S*,3*R*)-3,5-dimethyldehydro norleucine (dmdhNle) cannot be directly prepared via asymmetric sigmatropic rearrangements,[12] so they are typically made via chiral aldehydic intermediates prone to racemization.[7a,b,13] To circumvent this liability, we contemplated olefin cross metathesis (CM) under neutral conditions to install the alkene functionality.[14] The synthesis commenced with commercially available sulfinamide (**5**), which can also be easily prepared by a one-step diastereoselective amidoallylation reaction.[15] Replacement of the sulfinamide by a Fmoc protecting group, followed by a CM reaction, furnished building block **7** in only three steps from commercial material (**5**) (Scheme 2).

Scheme 2. Synthesis of Fmoc-dmdhNle-OH 7



There are multiple reports on the synthesis of (2*S*,4*R*)-*N*-methyl hydroxyleucine (*N*-Me HyLeu).[7a,b,13,16] In all cases, chiral reactants with one of the two stereocenters were subjected to asymmetric reactions. The *α*-carbon's stereochemistry has been set via catalytic asymmetric hydrogenation or asymmetric azidation via a chiral auxiliary.[7a,b,13] Alternatively, reactants with chiral centers at the *α*-carbon have been subjected to substrate-controlled methylation or hydrogenation to set configuration at the *γ*-carbon.[16] The lengthy synthetic routes,[7b,13,16b] challenging separation of the products,[16a] and utilization of reactions that are difficult to execute on a large scale[7a] motivated us to develop a new route. To circumvent the labilities, we developed a route to the protected *N*-Me HyLeu capitalizing on an asymmetric alkylation via Schöllkopf's chiral auxiliary, which has proven to be a powerful tool for setting the stereochemistry of the *α*-carbon of amino acids in excellent diastereoselectivity.[17] In that context, we effected diastereoselective alkylation of the eponymous chiral bis-lactim ether **8**[18] with chiral alkyl bromide **9**[19] yielding intermediate **10**. Removal of the chiral auxiliary yielded *O*- and carboxy-protected intermediate **11**. *N*-Boc protection followed by hydrolysis of the methyl ester set the stage for a chemoselective and quantitative *N*-methylation.[16b,20] The base-stable, Boc-protecting group of that was needed for the *N*-methylation was interconverted to Fmoc (Scheme 3), which was required for our planned solid-phase peptide synthesis.

The synthesis of the Fmoc-(2*S*,3*R*)-*β*-hydroxy tryptophan (Fmoc-HyTrp-OH) building block is inherently challenging due to its well-documented lability under both acidic and basic conditions.[6,7,13,21] In the published routes to this molecule, the stereochemistry of the 1,2-amino alcohol was established via either Sharpless amino hydroxylation of an elaborated *α*,*β*-unsaturated indole ester[7b,13] or the addition of metalated indoles to chiral amino aldehydes.[7a,d] The large number of steps, suboptimal regioselectivity of the aminohydroxylation, the obligate use of racemization-prone aldehyde intermediates, and the incompatibility of the published route for the preparation of HyTrp having an *S*-epoxide warranted the development of a new route. In a simpler route, we chose a diastereoselective aldol reaction using the Schöllkopf auxiliary to set the 1,2-amino alcohol stereochemistry. In this case, Schöllkopf's method was given its high stereocontrol, straightforward diastereomeric separation, and the mild conditions for chiral auxiliary removal.[17,22] Nevertheless, reactivity concerns prompted us to protect the indole nitrogen

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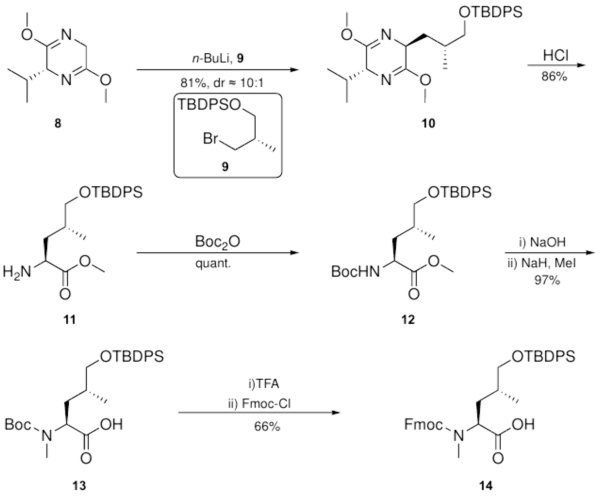
Org. Lett. 2024, 26, 9698−9703

Scheme 3. Synthesis of Fmoc-*N*-Me-HyLeu-OH 14

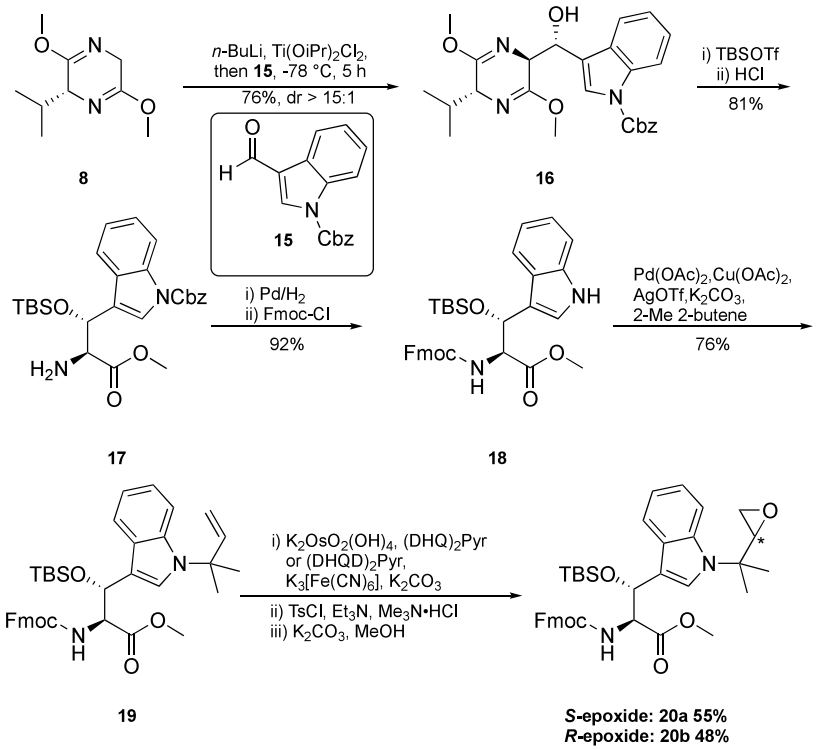


of the aldehyde reactant with a Cbz group.[23] A late-stage Sharpless asymmetric dihydroxylation was envisioned to provide either the *R*- or *S*-epoxide. We anticipated that selecting those conditions and reagents would minimize side reactions of HyTrp, while allowing us to prepare *tert*-prenyl and both epimers of epoxy HyTrp.

In the synthetic scheme, bis-lactim ether **8** was deprotonated by *n*-BuLi followed by transmetalation with $TiCl_2(OiPr)_2$, after which the solution of aldehyde **15** was added. The desired *syn* addition aldol product **16** was formed in 79% yield with high diastereoselectivity based on a presumptive 'tight titanium transition state'.[17a,24] The undesired (*S*,*S*) alcohol was formed in low yield (<10% yield), but could be removed by column chromatography. Due to the problematic hydrolytic auxiliary removal of the free aldol products generated via Schöllkopf's method,[25] we first protected the alcohol with a silyl group prior to hydrolysis, which yielded amino methyl ester **17**. Subsequent hydrogenation and Fmoc-protection delivered Fmoc-HyTrp-OMe **18**. The *tert*-prenyl group on the indole was installed via a modification of Baran's base-free protocol.[26] In this case, it was necessary to include K_2CO_3 (1.2 equiv) to neutralize the acid generated during Pd-catalyzed prenylation that could effect the decomposition of reactant **18** and product **19**.[27] Preparation of the chiral epoxides was achieved via asymmetric Sharpless dihydroxylations (89% and 82% yield with ∼10:1 diastereoselectivity for *S*- or *R*- diastereomer, respectively), followed by tosylation and ring closure.[7a−c] To our delight, the optically pure tosylate intermediate could be purified via column chromatography prior to epoxide formation, enabling epoxy Fmoc-HyTrp-OMe **20a** and **20b** to be prepared in 55% and 48% yield over three steps (Scheme 4). Whereas (2*S*,3*R*)-*β*-hydroxy tryptophan (HyTrp) is inherently unstable, *N*- and *O*-protected precursors (**19** and **20**) could be stored in a freezer for at least six months without noticeable decomposition. Because conventional conditions for saponification (*i.e.*, LiOH and NaOH) led to problematic elimination of the *β*-hydroxy functionality in the desired Fmoc-protected building block for peptide synthesis,[7a,13] we turned to a Me_3SnOH protocol that substantially suppressed the undesired side reaction.[28] In any case, saponification of **19** and **20** was executed right before the solid-phase peptide synthesis (see Supporting Information).

Having the amino acids, we envisioned syntheses of macrocyclization substrates via Fmoc-SPPS followed by peptide release and ring closure in solution. The optimal cyclization site reported in the solution-phase syntheses guided our SPPS.[7a,13] Bulky 2-chlorotrityl chloride (CTC) resin was utilized as the solid support because (i) it could minimize the potential diketopiperazine formation[29] and (ii) permits peptide

Scheme 4. Syntheses of Fmoc-HyTrp-OH 19, 20a, and 20b



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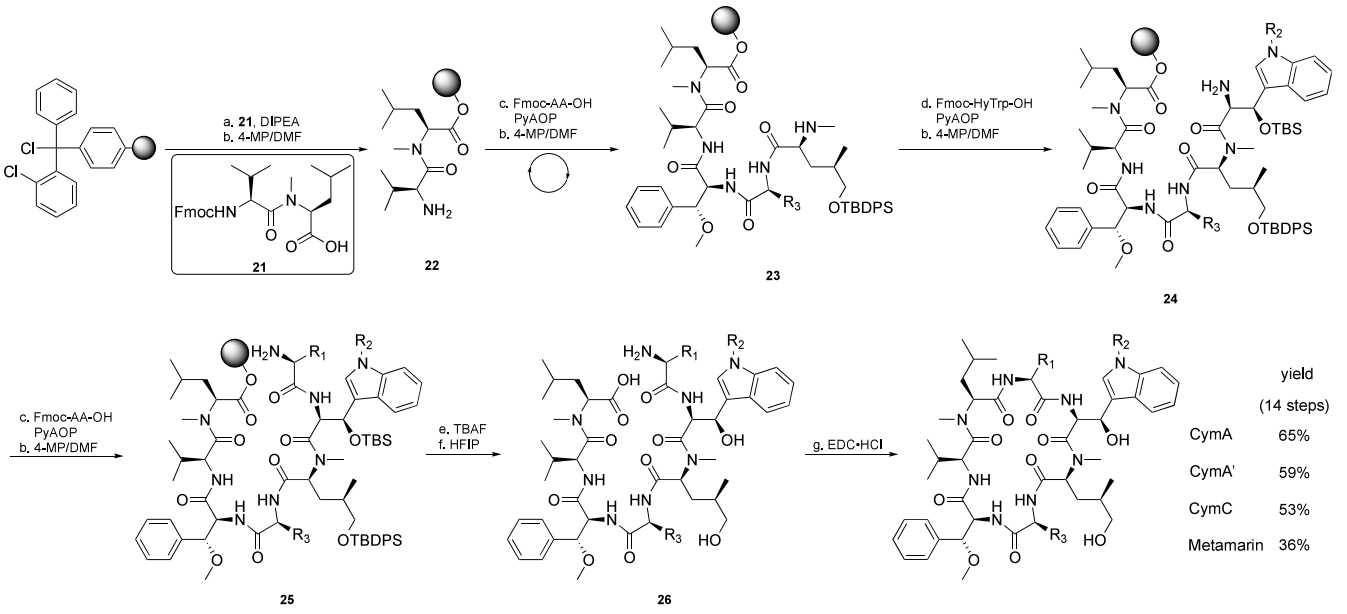
Scheme 5. Syntheses of Cyclomarin A, A′, C, and Metamarin



release under mild conditions[30] that are compatible with the acid-labile HyTrp. Initially, we found that the coupling between Fmoc-Val-OH and resin-bound *N*-Me Leu had to be left overnight for completion; thus, dipeptide Fmoc-Val-*N*-Me-Leu-OH **21** was directly loaded onto the CTC resin. Subsequently, Fmoc was removed with 20% 4-methylpiperidine (4-MP) in DMF to yield resin-bound dipeptide **22**. This dipeptide was elongated via three iterative cycles of couplings of amino acid building blocks with PyAOP followed by Fmoc deprotections to yield pentapeptide **23**. The intermediate was coupled with 2.5 equiv of crude Fmoc-HyTrp-OH using PyAOP in an overnight reaction given two considerations: (i) the attenuated reactivity of *N*-Me HyLeu and (ii) the instabilities of the high value HyTrps. The resulting hexapeptides were subjected to conventional deprotection and coupling with Fmoc-dmdhNle-OH **7**, yielding *O*-silyl protected heptapeptides **25**.

Given challenges in removing silyl protecting groups from the cyclomarins,[7a,13] we envisioned on-resin desilylation, product release, and macrocyclization. Interestingly, the desilylation of **25** was not trivial, requiring reaction optimization. For instance, the retro-aldol byproduct was observed upon prolonged TBAF treatment (see Supporting Information). We were gratified that removal of TBS and TBDPS groups could be easily achieved by TBAF treatment within 6 h to yield the linear precursors of CymA, CymA′, and CymC without epoxide opening. In contrast, desilylation of the linear precursor of Metamarin required 20 h. The fully deprotected heptapeptides were cleaved from the resin with 25% HFIP in DCM to yield the linear peptides **26**.[30] An EDC/HOBt/DIPEA protocol enabled macrocyclizations of linear heptapeptides under high dilution conditions. Starting with resin-bound Fmoc-Val-*N*-Me-Leu, we were gratified that overall yields in the syntheses of CymA, CymA′, and CymC were 65%, 59%, and 53%, respectively, without notable epimerizations. Despite the same SPPS strategy, the synthesis of Metamarin was less efficient (36% overall yield) due to epimerization in the macrocyclization step that necessitated HPLC purification. The comparatively low yield and epimer formation in the Metamarin cyclization indicate the dmdhNle residue present in the cyclomarins facilitates cyclization under the influence of 1,3-allylic strain (Scheme 5).

Reports of the antimicrobial activities of the natural products prompted assessments of the antimycobacterial and anti-*Plasmodium* activities of the synthetic cycloheptapeptides. We deemed these experiments important because they would provide further validation of the syntheses and to enable side-by-side comparisons of their activities for the first time in the literature (Table 1). Metamarin exhibited moderate anti-

Table 1. *In Vitro* Activities of CymA, CymA′, CymC, and Metamarin against *Mycobacterium tuberculosis* H37Rv and *Plasmodium falciparum* W2

Compound	*Mtb* MIC_{90} (nM)	*Pf* IC_{50} (nM)
CymA	60−120	98
CymA′	30	36
CymC	240	36
Metamarin	985−1970	197

mycobacterial activity compared to CymC and CymA, indicating the importance of dmdhNle residue. The epoxide moiety was important for their bioactivities as evidenced by the superior bioactivity of CymA compared to CymC. Interestingly, in *M. tuberculosis*, CymA is less potent than the structurally mis-assigned epimer CymA′, which indicates that the stereochemistry of the epoxide is important in bioactivity. The antimicrobial activities of our synthetic compounds are mostly consistent with those reported in the literature;[3,6] any deviations could reflect differences in strains or assay conditions (see Supporting Information).

In summary, new synthetic approaches to four chiral amino acids and a Fmoc-SPPS protocol for cyclomarins and Metamarin were developed. The strength of our synthetic strategy is its efficiency. Amino acid building blocks can be prepared from commercially available starting materials[31] in fewer steps than published syntheses: MeOPhe[7a,10,13] in three steps, dmdhNle[7a,b,13] in three steps, and the three HyTrp congeners[7,13,21b] in seven to ten steps. Though the disclosed

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synthesis of *N*-Me HyLeu has more steps than that published previously,[7a] the advantage of our seven-step route to the amino acid is its avoidance of a high-pressure hydrogenation that is only practical on a small scale. Aside from the amino acid syntheses, efficiency is also evidenced in that our syntheses require only a single chromatographic step and can be realized in 3 days. Structure−activity relationship studies of all of these cycloheptapeptides are underway in our laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03473.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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