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A Contribution to the Nomenclature of Depsipeptides

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Abstract: Depsipeptides, also called peptolides, are a class of peptidic compounds in which an amide bond has been replaced with an ester bond. The literature does not clearly display rules for the nomenclature of such compounds. Here a method is proposed to transcribe drawn depsipeptide structures in one-line text.

Keywords: depsipeptides; peptolides; nomenclature

Depsipeptides are heterodetic peptides in which at least one amide bond has been replaced with an ester bond. Depsipeptides include homomeric *O*-peptides and peptide lactones of hydroxyamino acids such as Ser, Thr, etc. and heteromeric peptides characterized by the replacement of some of the amino acids by hydroxy acids, also called peptolides. For the latter, the three letter nomenclature is frequently used and clearly suggests the sequence of the amino acids and hydroxy acids. The literature survey showed with little exception [1,2] that the use of the three letter nomenclature for the "side-chain built depsipeptides" is avoided. Our interest in cyclodepsipeptides containing the sequence Ala-Thr, in which the depsi bond is formed between the side-chain of *N*-*Z* protected Thr and the Ala carboxyl group, prompted us to develop a generic nomenclature which allows their one-line symbolic representation.

Abbreviations: But, butyric acid; Ahp, 3-amino-6-hydroxy-2-oxo-1-piperidine; cmTyr, 3′-chloro-*N*-methyl-Tyr; 5-MeHex, acid 5-methylhexanoic; PG, protecting group.

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Following the IUPAC-IUB recommendations [3–11] the linear depsipeptide including the above mentioned sequence should be represented as shown in Figure 1.

Since these symbolic representations normally require a chemical structure editor, it is probably best in general not to restrict oneself to one line (Figure 1a) but to follow Figure 1b. This would prevent the superfluous use of chemical bonds, as can be seen, for example, in the representation of the scyptolin B (Figure 2), a cyclodepsipeptide isolated from axenic cultures of the terrestrial cyanobacterium *Scytonema hofmanni* PCC [12]. The three letter nomenclature provided by the authors [1,12] was preserved. Although it is not the purpose of the present paper, it is noteworthy to mention that according to the existing nomenclature principles, **cmTyr** is actually **MeTyr(3–Cl)**. The abbreviation **But** should not be confused with butyl or *t*-butyl, since the notation has been already used in peptide and protein chemistry to improperly define those chemical groups [13,14]. The abbreviation **Ahp** might be also confusing. Logically interpreted, the symbolic representation Ahp^{6}–Thr^{7} implies an N-N bond, a feature that is not present in the structure of scyptolin B (Figure 2). In our view, this part of the molecule is a proper α-amino acid with an aldehydic

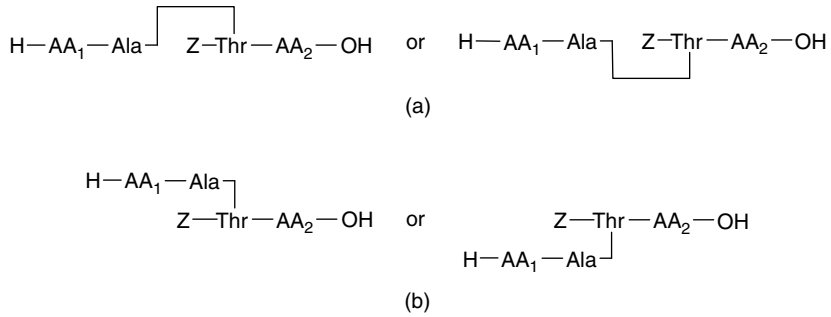


Figure 1

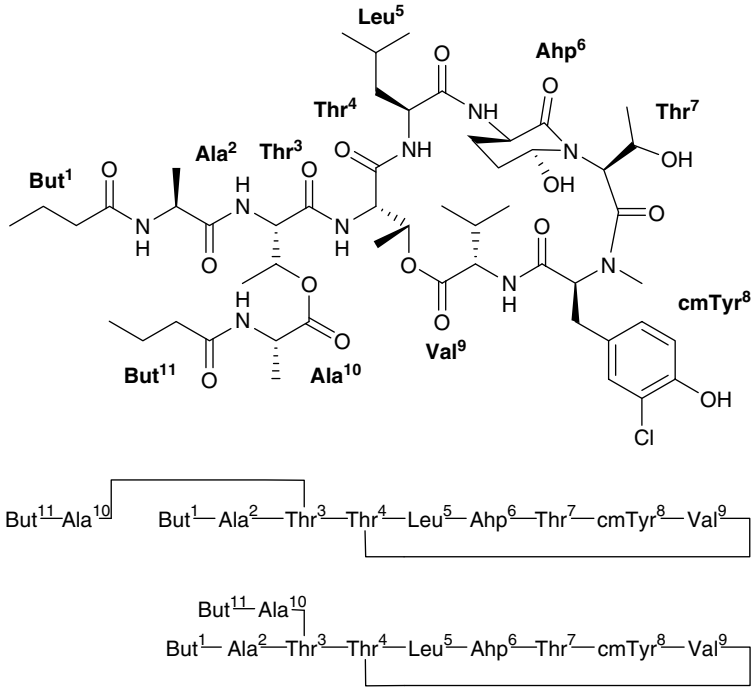


Figure 2

side chain, cyclized on the nitrogen of Thr. In this case, the nitrogen atom does not belong to the piperidine ring, but clearly to the amino functionality of Thr.

The above graphical representations (Figures 1 and 2) are rather difficult to draw in a textual form. A preliminary approach would be to write the side chain substituent between brackets as recommended by IUPAC-IUB [3–11]. In this way, the model depsi sequence (Figure 1) can be written as displayed in Figure 3.

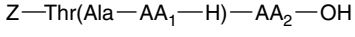
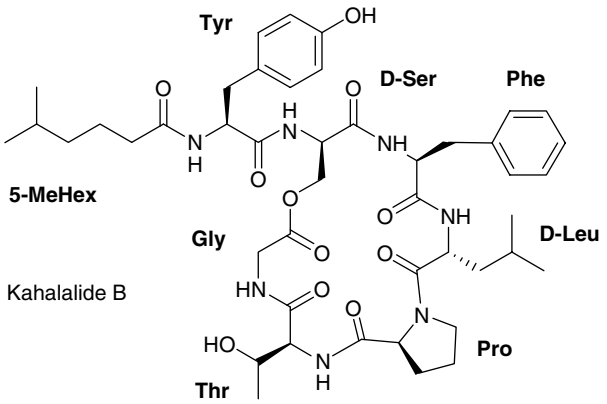


Figure 3

This solution was adopted by Albericio *et al.* [1] to symbolize the linear precursor of the cyclodepsipeptide kahalalide B (Figure 4).

A careful examination of the amino acid sequence written in one line shows that it is inaccurate, since it imposes the amino termini of AA_1 (Figure 3) or Gly (Figure 4) on the right. A more acceptable nomenclature would have the bracketed amino acid sequence inverted (Figure 5), which still suffers from imperfection, since does not respect the direct connection between Thr and Ala, or DSer and Gly (in kahalalide B).

A second approach, recommended by IUPAC-IUB [3–11], is to use the Ψ (psi) nomenclature for the one-line symbolism of the pseudopeptides. The



Kahalalide B

Linear precursor[1] of Kahalalide B:

5-MeHex—Tyr—DSer(Gly—H)—Phe—DLeu—Pro—Thr—OH

Figure 4

Z—Thr(H—AA_1—Ala)—AA_2—OH

5-MeHex—Tyr—DSer(H—Gly)—Phe—DLeu—Pro—Thr—OH

Figure 5

H—AA_1—Ala—(Z)Thr—AA_2—OH

Figure 6

Greek letter Ψ (psi) conveys the fact that a peptide bond has been replaced by a pseudopeptide bond, i.e. ester bond in the case of depsipeptides. The notation Ψ(CO-O) is applicable for depsipeptides containing hydroxy acids or amino unprotected Thr or Ser, which contributes *via* their side-chain to the ester bond formation. The IUPAC-IUB recommendation for the nomenclature of pseudopeptides [3–11] does not mention where an amino protecting group should be written if present.

Therefore, a simple alternative to this inconvenience is proposed by writing the amino substituent between brackets as shown in Figure 6. Such a nomenclature might be generally used to symbolize a depsipeptide containing Thr, Ser or any hydroxy-amino acid as a backbone component.

This representation respects the compulsory left location of the amino protecting group and undoubtedly suggests the presence of the depsi bond, since there is only one way left to connect both amino acid residues. Therefore, the use of Ψ (psi) symbolism here is superfluous. The advantage of the proposed notation can be envisioned when another depsi bond is present in the structure of depsipeptide, e.g. between Thr carboxyl group and AA_2 side chain, where AA_2 = Boc-Thr-OH (Figure 7).

H—AA_1—Ala—(Z)(αMe)Thr—(Boc)Thr—OH

Figure 8

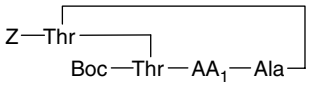


Figure 9

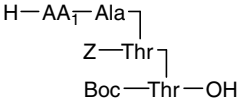
cyclo-[(Z)Thr—(Boc)Thr—AA_1—Ala]

Figure 10

cyclo-[(H)Thr—(H)Thr—AA_1—Ala]

Figure 11

IUPAC-IUB 1983 Recommendations:



(a)

Z—Thr(Ala—AA_1—H)—Thr(Boc)—OH

(b)

Proposed nomenclature:

Boc—Thr[Z—Thr(Ala—AA_1—H)]—OH

(c)

H—AA_1—Ala—(Z)Thr—(Boc)Thr—OH

(d)

Figure 7

Scyptolin B	cyclo-{[But^{11}—Ala^{10}(But^{1}—Ala^{2})Thr^{3}]Thr^{4}—Leu^{5}—Ahp^{6}—Thr^{7}—cmTyr^{8}—Val^{9}}
Linear precursor of Kahalalide B	H—Gly—(5-MeHex—Tyr)DSer—Phe—DLeu—Pro—Thr—OH
Kahalalide B	cyclo-[Gly—(5-MeHex—Tyr)DSer—Phe—DLeu—Pro—Thr]

Figure 12

The notation from Figure 7a can be adopted when a graphical representation is required. The textual form shown in Figure 7b is incorrect, since it suggests that the Boc group is connected to the side chain of Thr. Figure 7c is correct but totally incomprehensible. The only acceptable one-line representation is that proposed in Figure 7d.

However, some authors have used brackets before the three letters symbol to indicate substitution in other ways. Thus, α-methylation has been noted (αMe)Xyz. The prefix α (alpha) clearly suggests the substitution on the carbon chain and its absence involves a substitution on the amino functionality. Therefore, when a PG-(αMe)Xyz amino acid is part of a depsipeptide backbone, two pairs of brackets may be used. In this case, the *N*-substituent will be written first (Figure 8).

Regarding the derived cyclic depsipeptide, the use of graphical form presented in Figure 9 is in agreement with the IUPAC-IUB recommendations [3–11].

However, a written representation of the above cyclic depsipeptide is unattainable without using the notation shown in Figure 7d. It implies that both Z and Boc amino protecting groups are bracketed and the amino acid sequence is preceded by the prefix *cyclo* (Figure 10).

The fully deprotected corresponding cyclodepsipeptide can be written as shown in Figure 11, a representation that does not require the use of Ψ (psi) symbolism.

Finally, using the nomenclature shown in Figure 10, scyptolin B and kahalalide B can be easily represented in one-line (Figure 12).

CONCLUSION

No clear rules could be established from the literature to write peptolide formulas in text. A method was developed to enable the transcript of drawn structures in one-line representations suitable for body text, in agreement with the known nomenclature convention for peptide chemistry.

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