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Tetrahedron: *Asymmetry* 18 (2007) 2001–2010
Tetrahedron: *Asymmetry*

Tetrahedron: *Asymmetry* report number 96

A compendium of sugar amino acids (SAA): scaffolds, peptide- and glyco-mimetics

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Received 15 June 2007; accepted 2 August 2007

Abstract—Sugar amino acids (SAAs) are carbohydrate derivatives bearing both amino and carboxylic acid functionalities. SAAs are very versatile conformationally biased building blocks amenable to serve as glyco- or peptidomimetics. The stereochemical arrangement of the substituents of the sugar ring, its ring-size as well as the presence of additional functional groups provides a plethora of possible combinations. In this overview the structures of oxygen heterocylic SAAs that have been reported thus far are provided, having 3, 4, 5, 6-membered rings as well as several bicyclic counterparts.

Contents

1. Introduction

Monosaccharides are inexpensive, readily available and versatile building blocks that have not only been used frequently for the synthesis of complex oligomers,[1] but also as starting materials for the construction of natural products[2] and as templates in combinatorial approaches towards drug discovery, to name a few.[3–5] Of particular interest are carbohydrate derivatives bearing an amino and a carboxylic acid functionality, also referred to as sugar amino acids (SAAs).[6] Via the proper spacing of the amino and carboxylic acid groups on the sugar core and the introduction of specific functionality at the sugar hydroxyls, or following a 'backbone' modification strategy, SAAs can be designed to resemble conformationally restricted dipeptides. The sugar ring of SAAs offers a conformational bias, dictated by its ring size and the stereochemical arrangement of its substituents, which can be fine-tuned to provide the appropriate structural behaviour as part of a linear- or cyclic oligopeptide or foldamer. Herein we expand upon the scope of the thus far reviewed SAAs[7] by focusing on the structures, and not their applications, of oxygen heterocycles having 3, 4, 5 and 6 ring atoms and their corresponding bicycles that are functionalized with one (or more) amino functionality and a carboxylic acid group (Fig. 1).

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0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2007.08.004

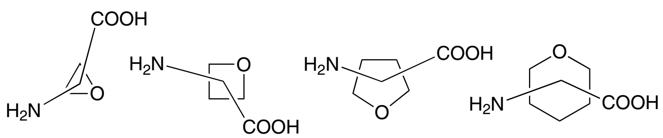


Figure 1. The generic structures of the four major type of oxygen heterocyclic sugar amino acids (SAAs) reviewed.

We have excluded cyclic amino acids [such as hydroxylated prolines, pipecolic or nipecotic acids] in which the amine function is part of a ring, as well as SAAs having no oxygen heterocyclic ring structure. Also not included are nucleoside amino acids, aza sugar amino acids, amino acid having sugars as side-chain and related natural products. We initially hoped to provide a comprehensive list of SAA scaffolds; however this is a fast expanding field and we are bound to have missed important contributions to the field. In order to ensure a comprehensive overview we urge readers to contact us—by e.mail or otherwise—and provide us with entries that will subsequently be included in a second collection of scaffolds.

2. Compendium

The structures of oxygen heterocylic SAAs (Fig. 2) that have been reported thus far are provided, having 3, 4, 5, 6- membered rings (Tables 1–4) as well as several bicyclic counterparts (Table 5).

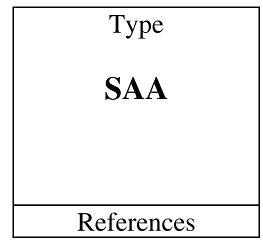


Figure 2. Overview of cyclic SAA scaffolds.

Table 1. Epoxide amino acids (depicted with unprotected amino and carboxylic acid functionalities, R′ = H or protecting group)

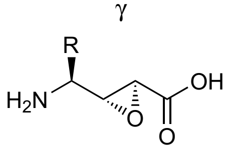
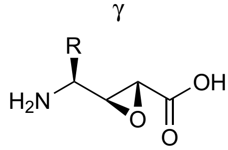
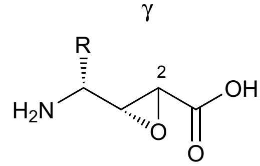
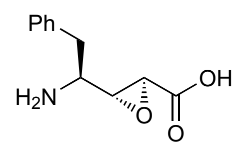
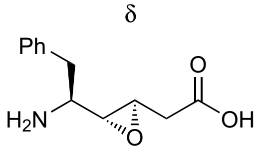
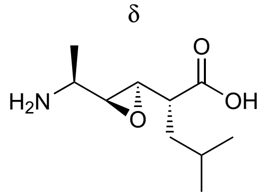
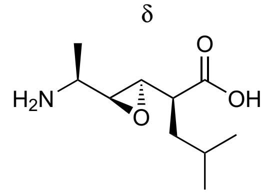
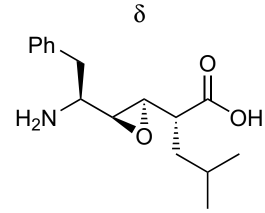
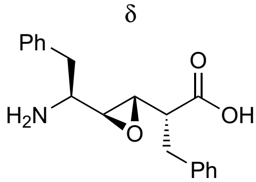
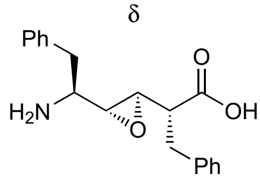
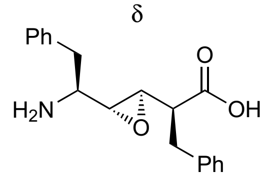
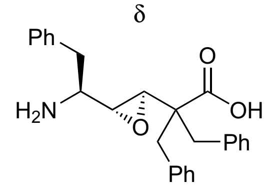
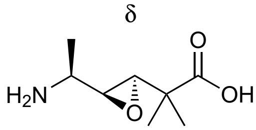
γ  R = H; Limberg et al.[8] R = *i*-Pr; Yoo et al.[9] R = Bn, Me, CH_2OR'; Reetz et al.[10]	γ  R = *i*-Bu, Bn, CH_2OR'; Yoo et al.[9]	γ  (2*R*), R = H; Limberg et al.[8] R = CH_2OR'; Langlois et al.[11–13] (2*S*); R = CH_2OR'Yoo et al.[9]	γ  Scholz et al.[14]
δ  Li et al.[15] Wiktelius et al.[17] Jenmalm et al.[18] *mix. of epox.*; Kaltenbronn et al.[16]	δ  Mann et al.[19]	δ  Mann et al.[19]	δ  Mann et al.[19]
δ  Jensen et al.[20] Wiktelius et al.[17]	δ  Jensen et al.[20] Wiktelius et al.[17] Jenmalm et al.[18]	δ  Wiktelius et al.[17] Jenmalm et al.[18]	δ  Wiktelius et al.[17] Jenmalm et al.[18]
δ  Mann et al.[19]			

Table 2. Oxetane amino acids (depicted with unprotected amino and carboxylic acid functionalities, R′ = H or protecting group)

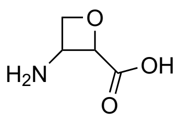
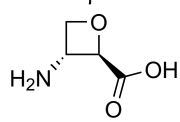
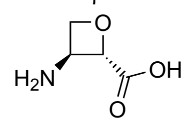
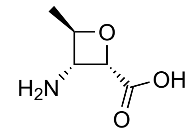
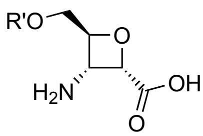
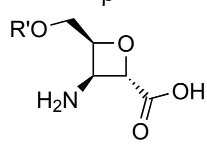
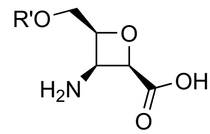
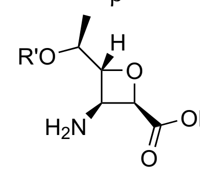
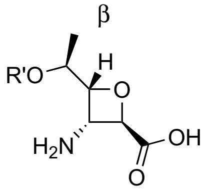
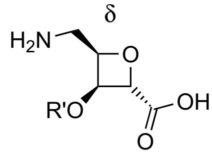
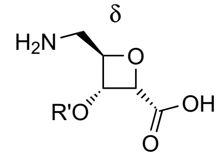
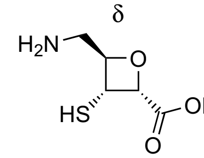
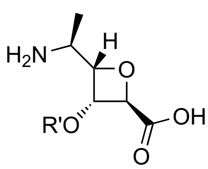
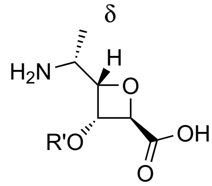
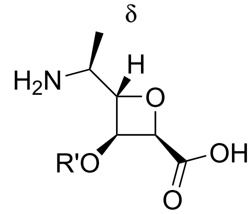
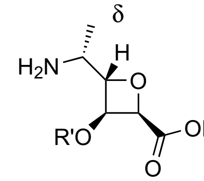
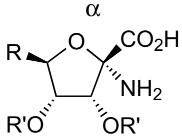
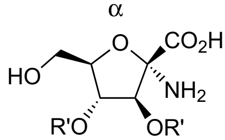
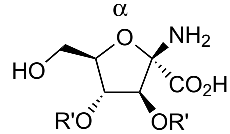
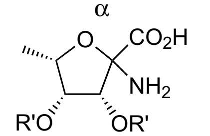
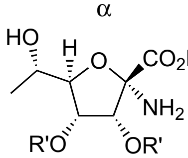
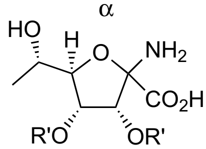
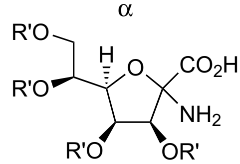
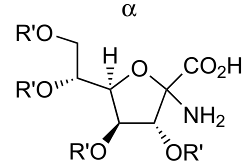
β  (*R*,*S*) and (*S*,*R*); Kawahata et al.[21] (±); Bach et al.[22]	β  Kawahata et al.[21]	β  Kawahata et al.[21]	β  Jenkinson et al.[23]
β  Jenkinson/Barker et al.[23,24] Elliott et al.[25] Wang et al.[26]	β  Jenkinson/Barker et al.[23,24]	β  Wang et al.[26]	β  Barker et al.[24] Claridge et al.[27]
β  Barker et al.[24] Johnson et al.[28]	δ  Johnson et al.[29–31]	δ  Johnson et al.[29]	δ  Sakya et al.[32]
δ  Johnson et al.[29–31] Fleet et al.[33]	δ  Johnson et al.[29–31] Fleet et al.[33]	δ  Johnson et al.[29–31]	δ  Johnson et al. [29–31]

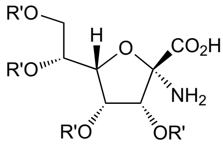
Table 3. Furanoid amino acids (depicted with unprotected amino and carboxylic acid functionalities, R′ = H or protecting group)

α  R = H, CH_2OR' Lakhrissi et al.[34]	α  Long et al.[35]	α  Long et al.[35]	α  Blériot et al.[36]
α  Estevez et al.[37,38]	α  (*R*/*S*); Estevez et al.[38]	α  (*R*/*S*); Estevez et al.[39] (*R*); Lakhrissi et al.[34] (*R*/*S*); Dondoniet al.[40]	α  (*R*/*S*); Brandstetter et al.[41]

(*continued on next page*)

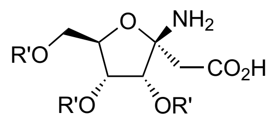
Table 3 (*continued*)

α



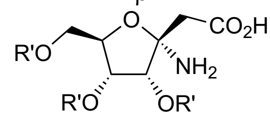
Lakhrissi et al.[34]

β



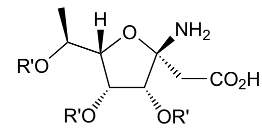
Taillefumier et al.[42,43]

β



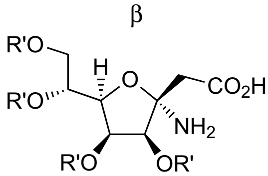
Taillefumier et al.[43]

β



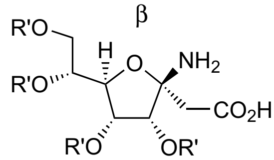
Taillefumier et al.[42]

β



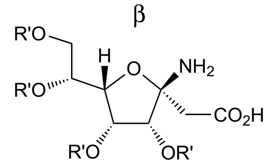
Taillefumier et al.[42,43]

β



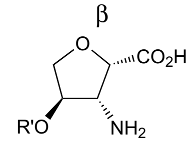
Taillefumier et al.[42,43]

β



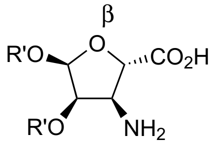
Taillefumier et al.[42,43]

β



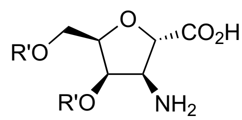
Sanjayan et al.[44]
Edwards et al.[45]

β



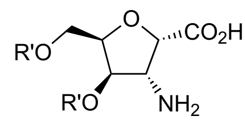
Gruner et al.[46,47]
McDevitt et al.[48]
Yamashita et al.[49]
Van Rompaey et al.[50]
DeNinno et al.[51]
Gao et al.[52]

β



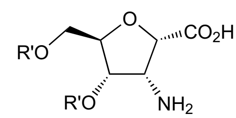
Watterson et al.[53]

β



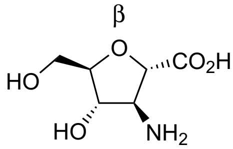
Watterson et al.[53]

β



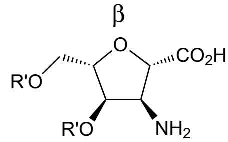
Watterson et al.[53]

β



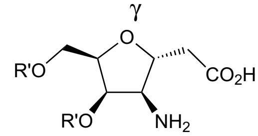
Watterson et al.[53]

β



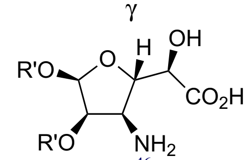
Hungerford et al.[54]

γ



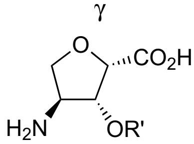
McDevitt et al.[48]

γ



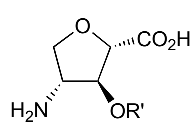
Gruner et al.[46]

γ



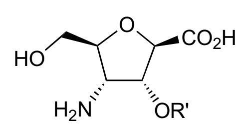
Sanjayan et al.[44]
Edwards et al.[45,55]

γ



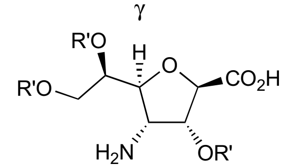
Sanjayan et al.[44]
Edwards et al.[45,55]

γ



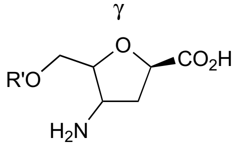
Hungerford et al.[54]

γ



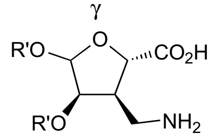
Hungerford et al.[54]

γ



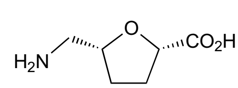
All isomers; Watterson et al.[56] and Edwards et al.[57]

γ



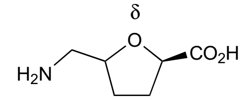
(*R*/*S*); Van Rompaey et al.[50]

δ



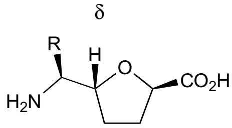
Chakraborty et al.[58]
Prasad et al.[59]

δ



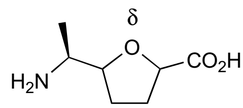
Both isomers; Chakraborty et al.[58,60]
(*S*); Prasad et al.[59]

δ



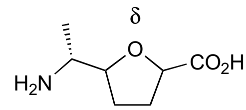
R = Me, Bn, $CHMe_2$, CH_2OR'; Chakraborty et al.[61]

δ



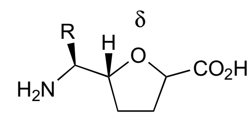
All isomers; Chakraborty et al.[62]
(*R*,*S*) and (*S*,*S*); Schrey et al.[63]

δ



(*R*,*S*) and (*S*,*S*); Chakraborty et al.[62]

δ



(*R*/*S*), R = $(CH_2)_3NH_2$
R = $(CH_2)_3NHC{=}NHNH_2$; Osterkamp et al.[64]

Table 3 (*continued*)

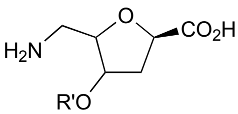
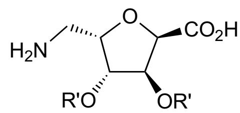
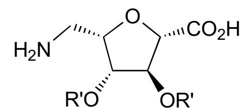
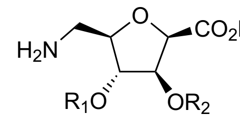
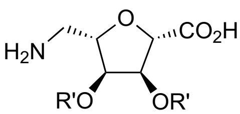
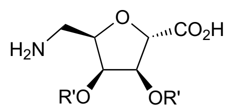
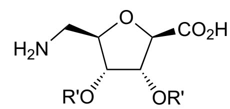
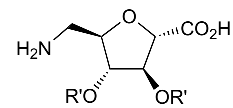
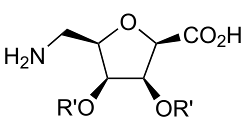
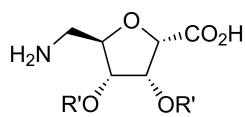
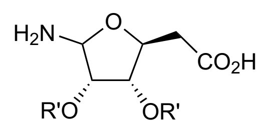
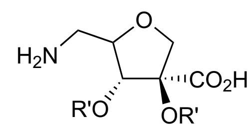
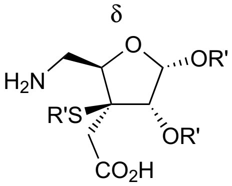
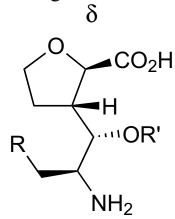
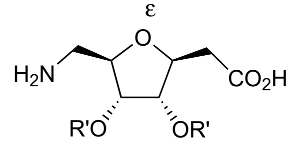
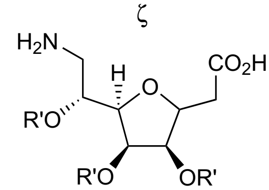
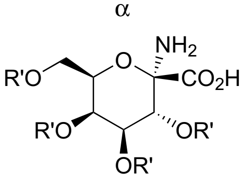
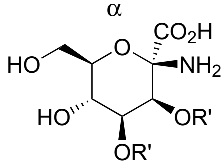
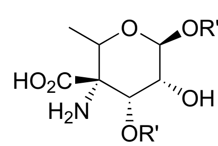
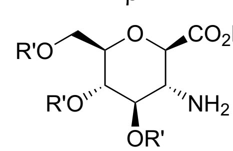
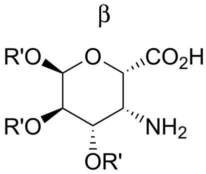
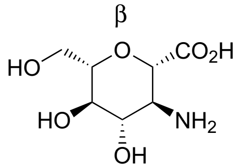
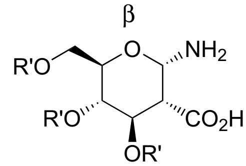
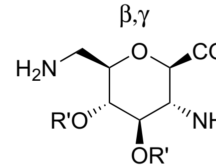
δ  All isomers; Watterson et al.[56] (*R*,*R*); Watkin et al.[65] (*S*,*S*); Edwards et al.[66]	δ  Chakraborty et al.[60]	δ  Poitout et al.[67]	δ  Poitout et al.[67] Chakraborty et al.[68,69] Grotenbreg et al.[70] R_1 = Aryl, R_2 = H; Grotenbreg et al.[71] Smith et al.[72,73] Long et al.[74] Brittain et al.[75]
δ  Long et al.[76] Hungerford et al.[77]	δ  Long et al.[76] Hungerford et al.[77] Claridge et al.[78]	δ  Long et al.[76] Hungerford et al.[77] Claridge et al.[78]	δ  Chakraborty et al.[60,79] Smith et al.[72]
δ  Brittain et al.[75]	δ  Hungerford et al.[77]	δ  Van Well et al. [80]	δ  (*R*) and (*S*): Simone et al.[81]
δ  McDevitt et al.[48]	δ  Hanessian et al.[82]	ε  McDevitt et al.[48] Van Well et al.[83–85]	ζ  (*R*) and (*S*); McDevitt et al.[48]

Table 4. Pyranoid amino acids (depicted with unprotected amino and carboxylic acid functionalities, R′ = H or protecting group)

α  Dondoni et al.[40]	α  Long et al.[86]	α  (*R*),(*S*) (*R*) and (*S*); Koos et al.[87]	β  Hoffman et al.[88] Von Roedern et al.[89] Kessler et al.[90] Haubner et al.[91] Suhara et al.[92–94]
β  Vogel et al.[95]	β  Lohof et al.[96]	β  Mostowicz et al.[97]	β,γ  Sicherl et al.[98] Grotenbreg et al.[99]

(*continued on next page*)

Table 4 (*continued*)

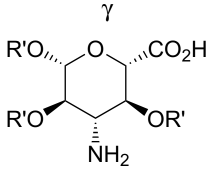
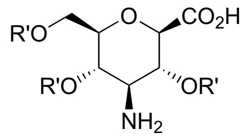
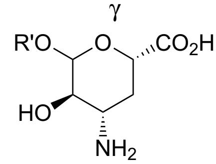
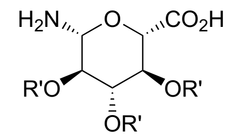
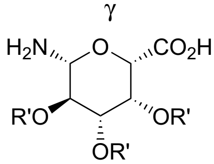
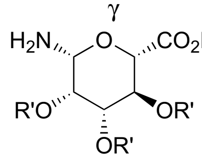
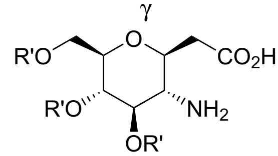
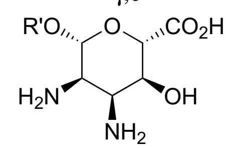
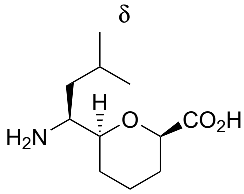
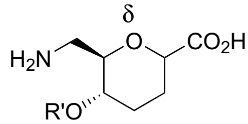
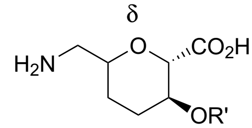
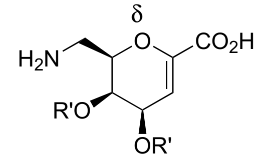
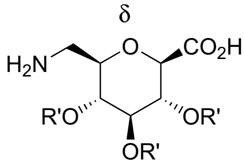
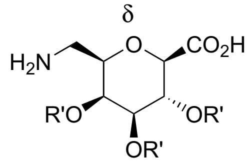
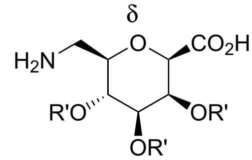
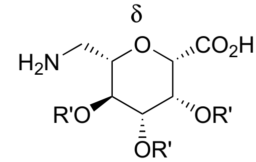
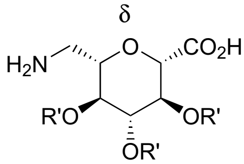
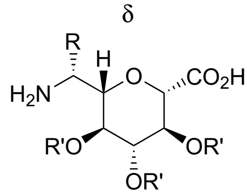
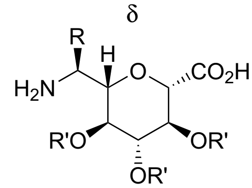
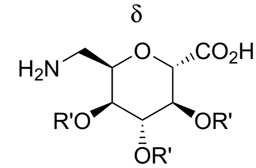
γ  Sofia et al.[100]	γ  Suhara et al.[93]	γ  (*R*) and (*S*); Sakata et al.[101]	γ  Nitta et al.[102] Györgydeák et al.[103] Drouillatet al.[104] Timmers et al.[105] von Roedern et al.[89] Kessler et al.[90]
γ  Györgydeák et al.[103]	γ  Revelskaya et al.[106]	γ  Kim et al.[107]	γ,δ  Hedenetz et al.[108]
δ  Schröder et al.[109]	δ  (*R*) and (*S*); Overkleeft et al.[110]	δ  (*R*) and (*S*): Grotenbreg et al.[99] Overkleeft et al.[110] El Oualid et al.[111–113] Aquilera et al.[114] IJsselstein et al.[115]	δ  Chung et al.[116]
δ  Fuchs et al.[117] Locardi et al.[118] Suhara et al.[119]	δ  Fuchs et al.[117]	δ  Lohof et al.[96] Haubner et al.[120]	δ  Haubner et al.[121] Fuchs et al.[122]
δ  von Roedern et al.[89,123] Kessler et al.[90] Lohof et al.[96] Stöckle et al.[124]	δ  R = Me, *i*Pr, Ph, Bn; Raunkjaer et al.[125]	δ  R = Me, *i*Pr, *i*Bu, Ph; Risseeuw et al.[126]	δ  Lohof et al.[96]

Table 4 (*continued*)

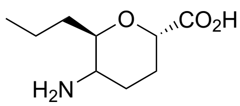
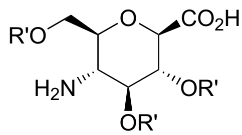
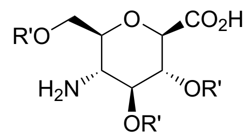
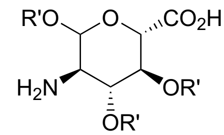
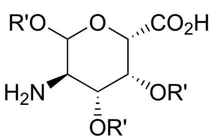
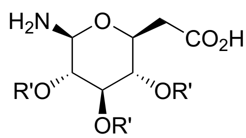
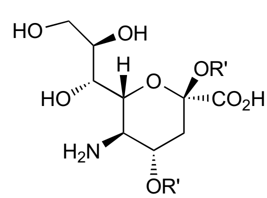
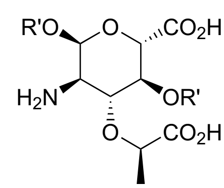
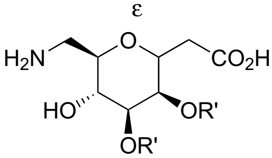
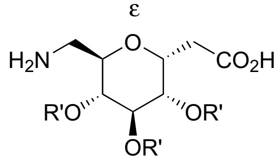
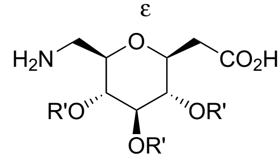
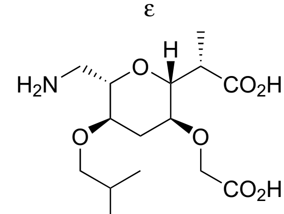
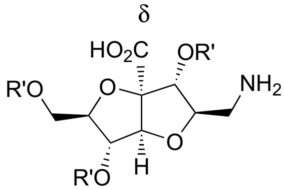
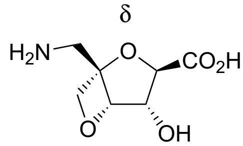
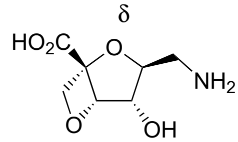
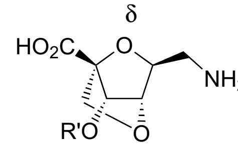
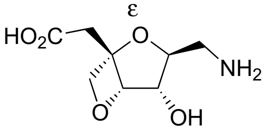
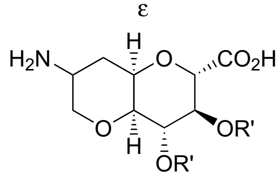
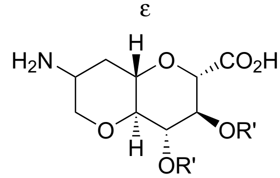
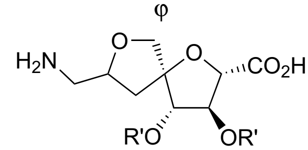
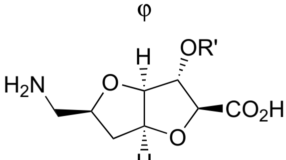
δ  (*R*) and (*S*); Kriek et al.[127]	δ  Fuchs et al.[128]	δ  Suhara et al.[93,94]	δ  Heyns et al.[129] Williamson et al.[130] Waltho et al.[131] Chan et al.[132] Sofia et al.[100] Billing et al.[133,134] Nishimura et al.[135] Müller et al.[136] von Roedern et al.[89] Kessler et al.[90]
δ  Heyns et al.[137]	δ  Van Well et al.[80]	δ  Szabo et al.[138] Gervay et al.[139] Ramamoorthy et al.[140] Sabesan et al.[141]	δ  Hecker et al.[142]
ε  (*R*) and (*S*); McDevitt et al.[48]	ε  McDevitt et al.[48]	ε  Van Well et al.[80]	ε  Smith III et al.[143]

Table 5. Bicyclic amino acids (depicted with unprotected amino and carboxylic acid functionalities, R′are protecting groups or hydrogens)

δ  Cipolla et al.[144]	δ  Van Well et al.[145]	δ  Van Well et al.[145]	δ  Verhagen et al.[146]
ε  Van Well et al.[145]	ε  (*R*) and (*S*); Grotenbreg et al.[147]	ε  (*R*) and (*S*); Risseeuw et al.[148]	φ  (*R*) and (*S*); Peri et al.[149] Cipolla et al.[144]
φ  Peri et al.[149]			

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