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Asymmetric and enantiospecific syntheses of 1-hydroxymethyl pyrrolizidine alkaloids

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ABSTRACT

Isoretronecanol and trachelantamidine (laburnine) are naturally occurring pyrrolizidine alkaloids which display potent biological activity, and as such these compounds have, in recent years, attracted significant interest from the bioorganic and synthetic communities. This review delineates both the asymmetric and enantiospecific syntheses of 1-hydroxymethyl pyrrolizidine alkaloids including isoretronecanol, trachelantamidine (laburnine) and related hydroxylated compounds.

Contents

1. Introduction

Azabicycles, such as pyrrolizidines **1**, indolizidines **2** and quinolizidines **3**, are commonly occurring structural motifs within natural products endowed with an extensive range of biological activities.[1] They all possess a bridge head nitrogen atom within a carbobicyclic ring system and, depending on the ring sizes and the number and position of hydroxyl or hydroxymethyl substituents, these compounds have different biological roles: for example, (+)-hyacinthacine A1 **4**[2] and (−)-lentiginosine **5**[3] are efficient glycosidase inhibitors, while (−)-lupinine **6** is a powerful bactericide.[4] Thus, there is significant interest in the development of efficient syntheses of these classes of compounds in enantiopure form (Fig. 1).

The 1-hydoxymethyl pyrrolizidines **7** are a sub-class of the pyrrolizidine alkaloids. (−)-Isoretronecanol **8** represents the simplest structure in this class, and was isolated from a genus of leguminous plant *Crotalaria spectabilis* and the seed of the *Crotalaria retusa* by Adams in 1942;[5] its enantiomer was isolated from *Lindelofia anchusoides* by Men'shikov in 1948.[6] The epimeric pyrrolizidines (−)-(1*R*,7a*S*)-**9** and (+)-(1*S*,7a*R*)-**9** were isolated from the

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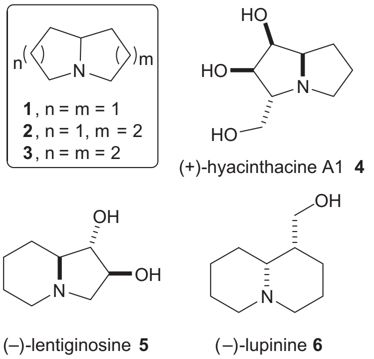

Figure 1. Representative pyrrolizidine, indolizidine and quinolizidine alkaloids.

overground parts of *Trachelanthus korolkovi fam* and *Cytisus laburnum*, and named (−)-trachelantamidine[7] and (+)-laburnine, respectively.[8] Furthermore, a number of alkaloids which include a 1-hydroxymethyl pyrrolizidine moiety (commonly known as a 'necine base') have been isolated.[9] For example, hastacine **19**, which bears a hastanecine **10** unit, was isolated in 1945 from *Cacalia hastate*, family Compositae (tribe Senecioneae),[10] and rosamarinine **20** was isolated in 1940 from *S. rosmarinifolius Linn.* (family Compositae).[11] To date, 12 naturally occurring (hydroxylated) 1-hydroxymethyl pyrrolizidines have been isolated, which include (−)-hastanecine **10**,[10] (−)-platynecine **11**,[12] (−)-rosmarinecine **12**,[11] (−)-turneforcidine **13**,[13] (+)-croalbinecine (helifoline) **14**,[14] (−)-petasinecine **15**,[15] (+)-macronecine **16**,[16] (−)-hadinecine **17**[17] and more recently transalpinecine **18**.[18] Their various biological properties have also been reported[19] which include carcinogenicity, hepatotoxicity and livestock poisoning.[20] In this review, asymmetric syntheses of these 1-hydroxymethyl pyrrolizidine alkaloids **8**–**18** will be discussed, highlighting the enantio- and diastereodefining steps in particular (Fig. 2).[21]

2. Asymmetric syntheses of isoretronecanol and trachelantamidine (laburnine)

The first preparation of the enantiopure antipodes of isoretronecanol **8** and trachelantamidine **9** was reported in 1977 by Vollhardt: a racemic diastereomeric mixture of ethyl pyrrolizidine-1-carboxylates was prepared and separated by chromatographic purification followed by classical resolution (diastereomeric salts formation with 3-bromo-camphorsulfonic acid followed by recrystallisation) to give both enantiomers of isoretronecanol **8** and trachelantamidine **9**.[22] Since then, various efforts towards asymmetric syntheses of isoretronecanol **8** and trachelantamidine **9** have appeared in the literature. For example, we have recently demonstrated the rapid construction of enantiopure pyrrolizidine scaffolds from 1-aminocyclohept-4-enes such as **24** and **25**. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide(*S*)-**22**[23] to α,β-unsaturated ester **21**, followed by alkylation of the resultant lithium (*Z*)-β-amino enolate[24] with allyl bromide, gave β-amino ester **23** in 60% yield and 85:15 dr. Treatment of **23** with Grubbs I catalyst gave **24** in 85:15 dr, and in 43% isolated yield (from **23**) and >99:1 dr after chromatographic purification. The C(1)-epimer **25** was also obtained in 80% yield and >99:1 dr by treatment of **24** (>99:1 dr) with KHMDS in ^{t}BuOH/THF. Alternatively, **25** could be prepared in 70% yield and >99:1 dr directly from **23**. The C(1)-epimeric substrates **24** and **25** were separately treated under our ammonium-directed oxidation conditions (HBF_4 and *m*-CPBA)[25] whereby protonation of the amino group with HBF_4 protects the nitrogen lone pair from oxidation, thus promoting oxidation of the olefin with *m*-CPBA.

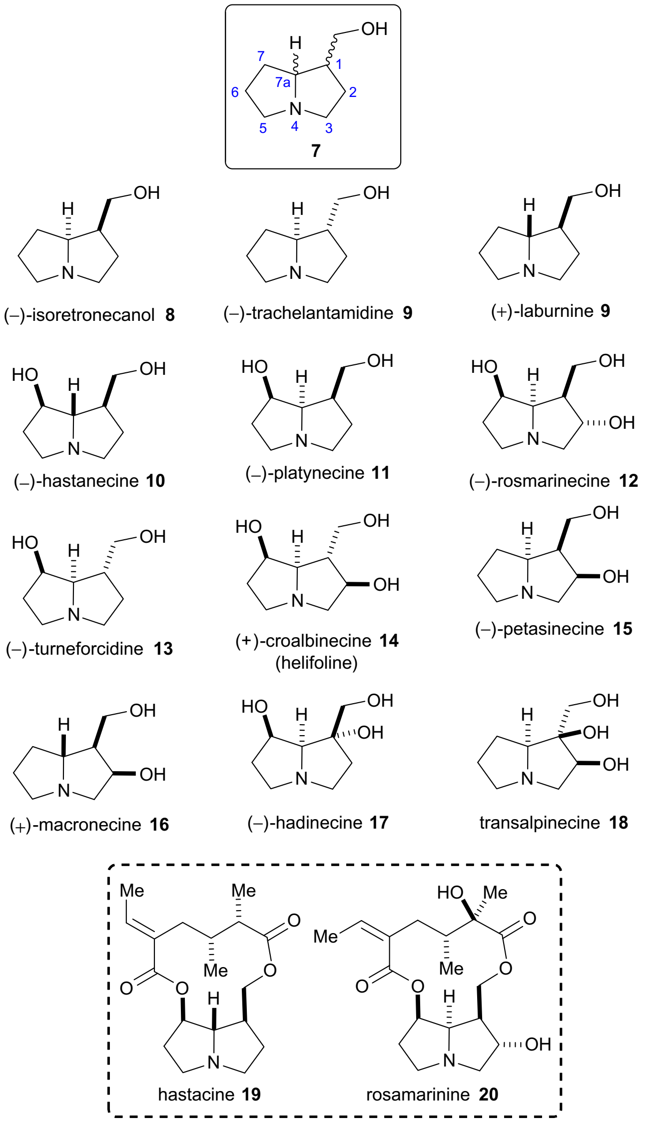

Figure 2. The structures of 1-hydroxymethyl pyrrolizidine alkaloids.

In the case of **25**, epoxidation occurs on the same face as the ammonium group due to hydrogen bonding with the peracid, followed by in situ acid-mediated ring-opening/lactonisation to give **27**, whereas for **24**, analogous treatment gave lactone **26**. In the latter case, the stereochemical outcome was proposed to be due to epoxidation of **24** occurring under steric control on the opposite face to both the bulky ammonium and *tert*-butyl ester groups. Reduction of **26** and **27** with $LiAlH_4$ gave triols **28** and **29** in 65 and 80% yield, respectively, from **24** and **25**. Treatment of **28** and **29** with $NaIO_4$ effected oxidative cleavage of the 1,2-diol units to give the corresponding dialdehydes, followed by hydrogenolytic removal of the *N*-protecting groups which facilitated in situ cyclisation/reduction of the resultant imines. After purification of the crude reaction mixtures on DOWEX ion exchange resin (−)-trachelantamidine **9** {$[\alpha]_D^{20}$ -13.0 (*c* 0.2 in EtOH)} and (−)-isoretronecanol **8** {$[\alpha]_D^{20}$ -70.5 (*c* 1.0 in EtOH)} were isolated in 62 and 65% yield, and >99:1 dr in each case (Scheme 1).[26]

2.1. Chiral auxiliary strategies

The use of chiral auxiliaries has been employed routinely in the asymmetric synthesis of natural and non-natural target molecules.