Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 66

Cascade cyclization and intramolecular nitrone dipolar cycloaddition and formal synthesis of 19-hydroxyibogamine†

Ziad T. I. Alkayar ‡ and Iain Coldham *

Received 14th November 2018,
Accepted 5th December 2018

DOI: 10.1039/c8ob02839g

rsc.li/obc

A cascade or domino sequence of condensation of hydroxylamine and an aldehyde to give an oxime, cyclization to a nitrone, and intramolecular 1,3-dipolar cycloaddition has been successfully employed where there is branching at C-4 as a route to the *iboga* alkaloids. Cyclization occurs with displacement of chloride as a leaving group and intramolecular cycloaddition occurs with an alkene as a dipolarophile. The reaction gives an azabicyclo[2.2.2]octane product containing a fused isoxazolidine as a single stereoisomer and this was converted to an isoquinuclidine that completed a formal synthesis of the alkaloid (±)-19-hydroxyibogamine.

Introduction

Iboga alkaloids have been isolated from plants of the *Tabernanthe* genus, found particularly in West Africa.[1] The *iboga* alkaloids are related by a common pentacyclic structure found in ibogamine **1**, that consists of an isoquinuclidine core with a fused indoloazepine ring and representative examples are shown in Fig. 1. Their pharmacological properties have been studied widely and they have attracted attention due to their ability to treat drug addiction.[2] Ibogaine **2** is the most abundant of the alkaloids in *Tabernanthe iboga* and has been used clinically. The alkaloid catharanthine **4** has potent antagonist activity against transient receptor potential melastatin 8 (TRPM8), which is expressed in sensory neurons and involved in thermoregulation and pain.[3] This compound is an important intermediate in the synthesis of vinblastine and analogues.[4]

Many syntheses of the alkaloid ibogamine have been reported.[5,6] In contrast, there is only one report of the preparation of the *iboga* alkaloid (–)-19-hydroxyibogamine **5**,[7] which shows marked antibiotic activity.[8] There is a growing number of *iboga* alkaloids with a hydroxyethyl group or other oxygenated side chain at C-20 of the core ring system.[9] Here we report an efficient synthesis of the isoquinuclidine core with a hydroxyethyl side chain that makes use of a nitrone cycloaddition as part of a cascade process involving simple condensation of hydroxylamine with an aldehyde followed by cyclization on to an alkyl halide and cycloaddition. We have applied this to a formal synthesis of 19-hydroxyibogamine **5**.

We have reported a number of examples of the formation of polycyclic amines by use of a cascade strategy that incorporates a condensation reaction of an amine and an aldehyde (or ketone) followed by *in situ* cyclization of the imine (or oxime or hydrazone) on to an alkyl halide, followed by *in situ* dipolar cycloaddition.[10–15] Our efforts have been centred mostly on fused ring systems (Scheme 1a) and this chemistry leads to the synthesis of several natural products (*aspidosperma* alkaloids, myrioxazine A).[10,11] An intermolecular cycloaddition alternatively leads to bicyclic products and has been used to prepare crispine A and macronecine.[12] We have extended the method-

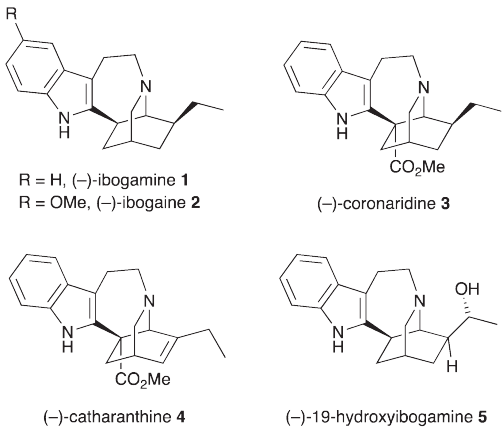

Fig. 1 Representative *iboga* alkaloids, **1–5**.

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK.
E-mail: i.coldham@sheffield.ac.uk

†Electronic supplementary information (ESI) available: Copies of NMR spectra and X-ray data. CCDC 1858480. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob02839g

‡New address: Department of Chemistry, University of Diyala, Diyala, Iraq.