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Digest paper

Synthesis of the sedum and related alkaloids: A personal perspective

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ABSTRACT

Significant recent contributions to the synthesis of the sedum alkaloids are discussed. Related compounds, such as pinidinol, porantheridine, dumetorine and the tetraponerines are also included. The syntheses are categorised according to the key motif or chemistry employed: isoxazolidines, metathesis, asymmetric aza-Michael, heterocycle lithiation, organocatalysis, aromatic heterocycles and chiral imines.

Contents

Introduction . . . 559
The isoxazolidine strategy . . . 560
Metathesis methods . . . 563
Asymmetric aza-Michael chemistry . . . 563
Lithiation . . . 564
Organocatalysis . . . 565
From aromatic heterocycles . . . 565
From chiral imines . . . 566
Outlook . . . 567
Acknowledgment . . . 567
References . . . 567

Introduction

Some years ago, we published a review of the synthesis of the sedum alkaloids,[1] and included a number of compounds that were synthetically if not biologically related. These included dumetorine, which shares the 1,3-aminoalcohol moiety, and the tetraponerines, which possess a corresponding 1,3-diamine moiety. This digest is not an attempt to review comprehensively all of the contributions to the area that have been made in the meantime, but to highlight some of the contributions that have greater significance in the author's opinion, naturally including those from this laboratory.

While some of the sedum alkaloids offer interesting biological properties, it is clear that the major reason for their synthesis is to test and to showcase new synthetic methodology. This digest article, therefore, focusses on a selection of those reports that do

Abbreviations: BIPHEPHOS, 6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[*d,f*][1,3,2]dioxaphosphepin); CDI, carbonyl diimidazole; DIAD, di-isopropylazodicarboxylate; DEAD, diethylazodicarboxylate; DMA, *N,N*-dimethylacetamide; IBX, 2-idoxybenzoic acid; mcpba, *m*-chloroperbenzoic acid; Me-CBS, 2-methyl-CBS oxaborolidine; Phth, phthaloyl; PMB, *p*-methoxybenzyl; PPTS, pyridinium *p*-toluenesulfonate; PS-PPTS, polymer supported pyridinium *p*-toluenesulfonate; p-TsOH, *p*-toluenesulfonic acid; TMG, tetramethyl guanidine.

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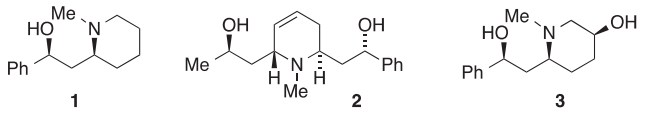


Fig. 1. Examples of sedum alkaloids.

so. Quite a number of reports of syntheses of sedum alkaloids offer little in the way of new chemistry and, therefore, are not discussed.

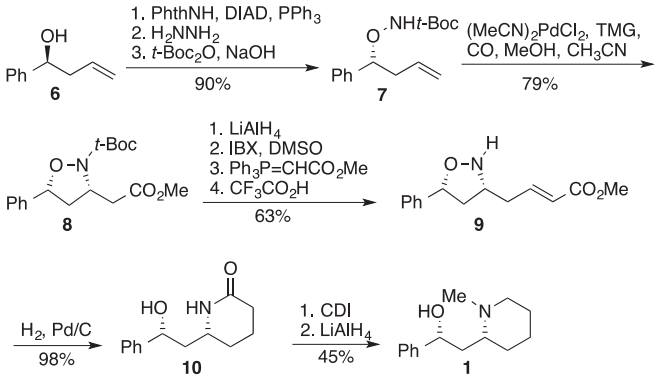
A second aspect of this area deserves comment. The sedum alkaloids come in two classes: the one-armed and the two-armed (Fig. 1). The former, such as sedamine **1**, have tended to be the subject of numerous syntheses. Much less work has been reported concerning the more complex two-armed sedum alkaloids, such as sedinine **2**. Given the inherently greater challenge presented by these more complex molecules, it would be gratifying to see, henceforth, more syntheses of these. If the methodology is good, shouldn't it be able to handle greater complexity? The same applies to the hydroxylated sedum alkaloids, in which alcohol substitution on the piperidine ring raises the level of synthetic challenge. 5-Hydroxysedamine **3** is an example of this class of compounds.

The isoxazolidine strategy

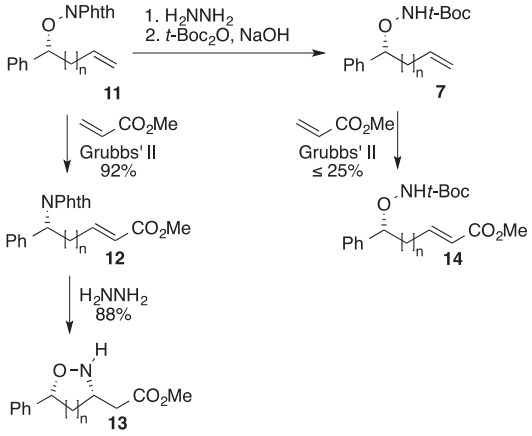
The synthesis of sedum alkaloids from isoxazolidines has been well established. The isoxazolidines were always prepared by a [3 + 2] dipolar cycloaddition of an alkene. This body of work, mostly from the laboratories of Hootelé and Tuffariello, was documented in the earlier review.[1] Cycloaddition chemistry leads to a single set of regio and stereoisomers, as well as usually giving a racemic product. Some years ago, therefore, we set about exploring non-cycloaddition approaches to isoxazolidines and, thence, sedum and other alkaloids. Our isoxazolidine route to sedum alkaloids arose out of consideration of using tethered functionalisation, in which a nucleophilic nitrogen is covalently bonded to an oxygen substituent through one or more atoms.[2] It was reasoned that the shortest possible tether between a nitrogen atom and an oxygen atom would be a sigma bond i.e. use a hydroxylamine (Scheme 1).

The first system developed was based upon the Semmelhack method[3] for cyclocarbonylation of alkenols. Indeed this system could be implemented using unsaturated hydroxylamines **4** with little change over that procedure: a palladium(II) catalyst to activate the alkene, a copper(II) co-oxidant, a base and carbon monoxide to provide the carbonyl group of the product. The reaction gave isoxazolidines **5** in good yield and high selectivity for the 3,5-*cis* isomer. While the initially proposed mechanism involved nucleophilic attack on a η^2-Pd complexed alkene (route A), elegant stereochemical studies by Kocovsky and Markov showed that it actually proceeds by migratory insertion of the alkene into a Pd-N bond (route B).[4]

The reaction was rapidly employed in a synthesis of sedamine **1** (Scheme 2).[5] All that was required was extension of the side chain



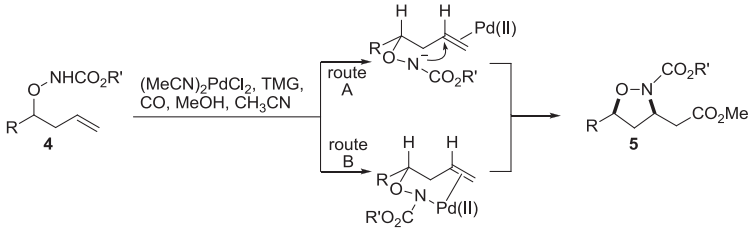
Scheme 2. A synthesis of sedamine.



Scheme 3. Isoxazolidines by the metathesis-Michael pathway.

of isoxazolidine **8** by conventional means to allow piperidine ring construction. This was achieved using Wittig chemistry and a tandem hydrogenation-lactamisation reaction which allowed three steps to be condensed into one. The resulting lactam **10** could then be converted into sedamine **1** by reduction. The isoxazolidines proved with time to be adept at tandem reactions triggered by reduction.

The principle drawback of this chemistry is the requirement to use more than two equivalents of copper(II) as a re-oxidant for palladium. This encouraged us to examine a more atom economical alternative. We reasoned that we could employ the same substrates, but subject them to cross-metathesis to convert the alkene into a Michael acceptor (Scheme 3). Treatment with base would then yield the desired heterocycle. In practice, however, the cross-metathesis reaction of Boc protected hydroxylamine **7** was highly inefficient due to competing and unexpected N-O bond cleavage! The solution was to take a step backwards. The corresponding N-phthaloyl derivatives **11** (which are actually



Scheme 1. Palladium catalysed isoxazole synthesis.