Tetrahedron 65 (2009) 10816–10829

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

SmI_2-mediated dialdehyde 'radical then aldol' cyclization cascades: a feasibility study

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ARTICLE INFO

Article history:
Received 31 July 2009
Received in revised form 24 August 2009
Accepted 7 September 2009
Available online 12 September 2009

Keywords:
Samarium
Radical
Cyclization
Cascade

ABSTRACT

Dialdehydes undergo 'radical then aldol' cyclization cascades upon treatment with SmI_2, generating four contiguous stereocenters with high diastereocontrol. The scope of the process has been explored and the cascade has been extended to also include lactone reduction.

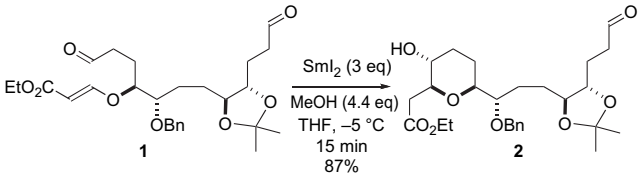
1. Introduction

Since its introduction to the synthetic community by Kagan, samarium(II) iodide (SmI_2) has become one of the most important reducing agents in organic synthesis.[1] The versatile, single electron-transfer reagent has been used to mediate many processes ranging from functional group interconversions to complex carbon–carbon bond-forming sequences.[1] In particular, cyclization reactions mediated by the reagent have met many synthetic challenges in natural product synthesis.[1f] In this context, we have introduced several stereoselective cyclizations using the lanthanide reagent in recent years.[2–6] Of the many reducing agents available to the synthetic chemist, SmI_2 is the one reagent able to orchestrate powerful sequential processes.[1a] The development of sequential reactions in which a number of transformations convert simple starting materials to complex products, using a single reagent, in a single synthetic operation, is one of the most important goals of the synthetic chemist.

Here we report in full our feasibility studies on the development of a dialdehyde cyclization cascade mediated by SmI_2 in which the aldehyde groups undergo stereoselective reaction in a programmed sequence to give complex products.[7]

2. Results and discussion

In 2002 Takahashi and Nakata described a synthesis of mucocin that involved the SmI_2-mediated, aldehyde–alkene cyclization of dialdehyde **1** to give **2** as the key step in their approach (Scheme 1).[8]



Scheme 1. Takahashi and Nakata's SmI_2-mediated cyclization en route to mucocin.

Carbonyl-alkene cyclizations using SmI_2 are believed to proceed by reduction of the aldehyde to the ketyl radical anion followed by addition to the alkene.[1,9] The transformation of **1** to **2** is therefore remarkable as only one aldehyde is reduced by the reagent. The authors observed that the use of excess SmI_2 or prolonged reaction times led to reduction of the second aldehyde and the formation of complex product mixtures. Intrigued by this result, we speculated that a new class of sequential cyclization mediated by SmI_2 might be possible using *dialdehyde* substrates: one aldehyde acts as a radical precursor while the other remains unreactive until late in the sequence when it behaves as an electrophile. We envisaged several classes of dialdehyde cascade from which we selected to study the feasibility of the sequence using substrates **3**. We proposed that aldehyde group 1 would react first through a facile 5-*exo*-*trig* radical cyclization while aldehyde group 2 waits in line. After radical cyclization, aldehyde group 2, in samarium enolates **4**,[10] would undergo aldol cyclization to form tricyclic systems **5** (Scheme 2).

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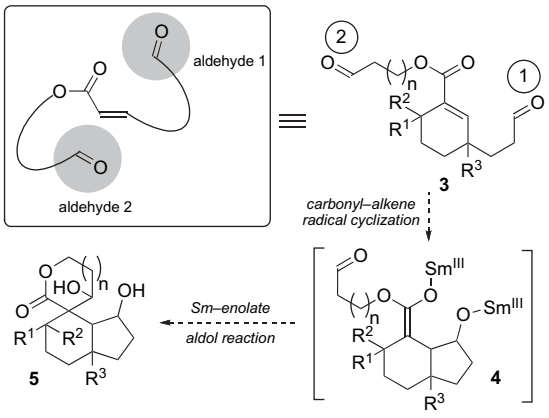
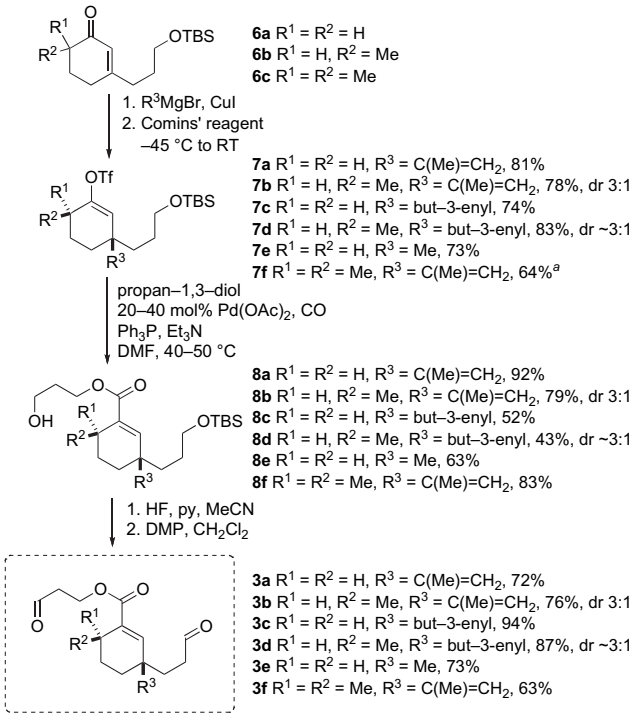
doi:10.1016/j.tet.2009.09.035



Scheme 2. Proposed sequential dialdehyde cyclizations mediated by SmI_2.

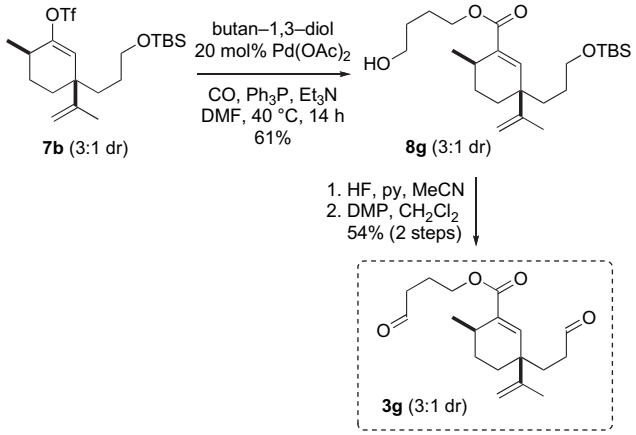
Although an example of a ketyl-olefin cyclization/*inter*molecular aldol sequence has been reported by Enholm,[11] to our knowledge, no intramolecular variants have been reported presumably as both aldehydes in the starting material would be expected to react with SmI_2 to give complex product mixtures. If successful, we anticipated that the sequential cyclizations of **3**, in which four contiguous stereocenters, including one quaternary stereocenter, are generated, would occur with high diastereocontrol.

We began by preparing a range of dialdehyde substrates **3** (n=1) by a modification of our previously reported route to related substrates.[6] Addition of an organocopper to cyclohexanones **6a–c** gave vinyl triflates **7a–f** after trapping of the intermediate enolates with Comins' reagent *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide).[12] Organocopper addition to cyclohexenone **6b** gave **7b** and **7d** as a 3:1 mixture of diastereoisomers. Palladium-catalyzed carbonylation in the presence of propan-1,3-diol gave esters **8a–f** in moderate to good yield. Deprotection and oxidation using the Dess–Martin periodinane[13] gave dialdehydes **3a–3f** (Scheme 3).



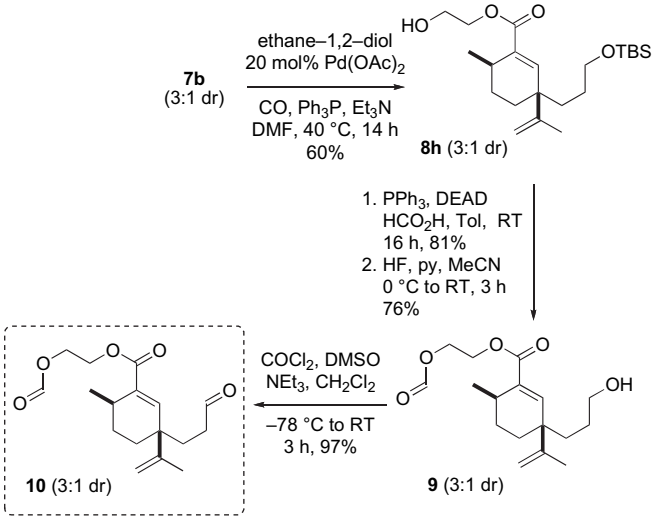
Scheme 3. Synthesis of dialdehyde cyclization substrates **3a–3f** (n=1). [a] **7f** was formed by cuprate addition (82%), followed by triflate formation in a separate step (LDA; Comins' reagent, 78%). Comins' reagent: *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide).

We have also prepared dialdehyde substrate **3g** (n=2) to investigate the feasibility of forming a seven-membered lactone ring in the second stage of the cascade (Scheme 4). Vinyl triflate **7b** underwent palladium-catalyzed carbonylation in the presence of butan-1,4-diol to give ester **8g** in 61%. Deprotection and oxidation gave dialdehyde **3g** in 54% yield (two steps).



Scheme 4. Synthesis of dialdehyde cyclization substrate **3g** (n=2).

Finally, we prepared formate **10** to investigate the possibility of trapping the Sm-enolate intermediate with a formate ester in a 'radical then Dieckman' cyclization cascade (Scheme 5). Palladium-catalyzed carbonylation of **7b** in the presence of ethane-1,2-diol gave ester **8h**. Mitsunobu reaction with formic acid was used to introduce the formate group[14] and deprotection of the silyl ether gave **9**. Finally, a Swern oxidation[15] gave formate-aldehyde **10** in excellent yield (Scheme 5).



Scheme 5. Synthesis of 'dialdehyde' cyclization substrate **10**.

With dialdehydes **3a–3f** in hand we investigated the proposed cyclization sequence. Pleasingly, upon treatment with SmI_2, dialdehydes **3a–3e** underwent double cyclization to give tricyclic products **5a–5e** in good yield and with excellent control in the construction of four stereocenters (Scheme 6).[16] The cyclization of **3b** and **3d**, 3:1 mixture of diastereoisomers, led to **5b** and **5d** as similar diastereoisomeric mixtures that were readily separated by chromatography. The structure of **5a** and **5b** was confirmed by X-ray crystallography (Scheme 6).[7]