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SmI_2-mediated dialdehyde cyclization cascades

Matthew D. Helm, David Sucunza, Madeleine Da Silva, Madeleine Helliwell, David J. Procter *

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

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ABSTRACT

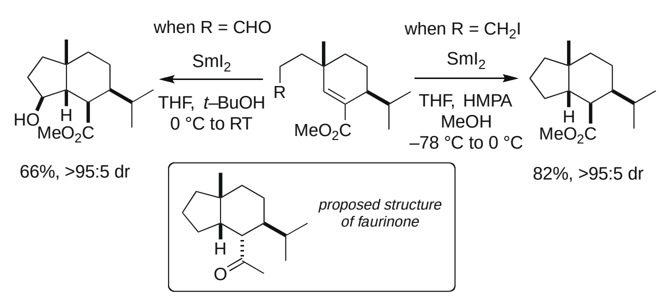
Dialdehydes undergo sequenced SmI_2-mediated cyclization cascades generating four contiguous stereocenters with high diastereocontrol.

Since its introduction to the synthetic community by Kagan, the one-electron reducing agent samarium(II) iodide (SmI_2) has found widespread use in organic synthesis.[1] The versatile reagent has been used to mediate many processes ranging from functional group interconversions to complex carbon–carbon bond-forming sequences.[1] Cyclization reactions mediated by SmI_2 are valuable tools for natural product synthesis.[1f]

We have introduced several stereoselective cyclizations using the lanthanide reagent. For example, we have developed a 4-*exo*-trig cyclization of γ,δ-unsaturated aldehydes to give *anti*-cyclobutanols[2] and have exploited this reaction in the synthesis of the pestalotiopsin skeleton.[3] We have also developed a conjugate reduction-aldol spirocyclization sequence for the stereoselective synthesis of oxa- and azaspirocycles[4] and have used this new transformation in an approach to stolonidiol.[5] Recently, we have reported a flexible approach to decorated *cis*-hydrindanes, a motif found in many biologically active natural products, which exploits highly diastereoselective SmI_2-mediated cyclizations of aldehyde and halide substrates.[6] The approach has been applied in the synthesis of the proposed structure of *rac*-faurinone (Scheme 1).[6]

In this Letter, we report our preliminary feasibility studies on the development of dialdehyde cyclization cascades mediated by SmI_2, in which the aldehyde groups undergo stereoselective reaction in a programmed sequence to give complex products.

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 2).[7]



Scheme 1. SmI_2-mediated cyclizations of aldehyde and halide substrates in an approach to decorated *cis*-hydrindanes.

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.[1,8] The transformation of **1** to **2** is, therefore, remarkable as only one aldehyde reacts while the other survives the reducing conditions. While the authors did not discuss this selectivity, they 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 where each aldehyde undergoes cyclization in a programmed sequence.

We selected dialdehyde substrates **3** for our study. We envisaged 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**,[9] would undergo aldol cyclization to form tricyclic systems **5** containing a *cis*-hydrindane core (Scheme 3).

* Corresponding author. Fax: +44 161 275 4939.
E-mail address: david.j.procter@manchester.ac.uk (D.J. Procter).

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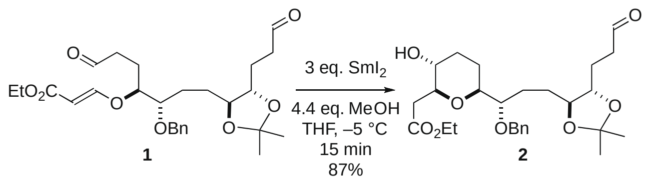


Scheme 2. Takahashi and Nakata's SmI_2-mediated cyclization *en route* to mucocin.

While an example of a ketyl-olefin cyclization/*inter*molecular aldol sequence has been reported by Enholm,[10] 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 (vide infra).

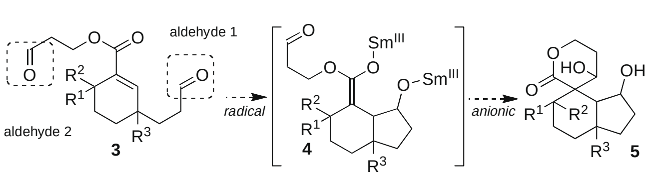
We began by preparing a range of dialdehyde substrates **3** by modifying our previously reported route to related substrates.[6] Addition of an organocopper to cyclohexanones **6a**–**c** gave vinyl triflates **7a**–**f** after trapping the intermediate enolates with Comins' reagent.[11] Organocopper 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[12] gave dialdehydes **3a**–**f** (Scheme 4).

With dialdehydes **3a**–**f** in hand, we investigated the proposed cyclization sequence. Pleasingly, upon treatment with SmI_2, dialdehydes **3a–e** underwent double cyclization to give tricyclic products **5a–e** in good yield and with excellent control in the construction of four stereocenters (Scheme 5).[13] 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 5).[14]

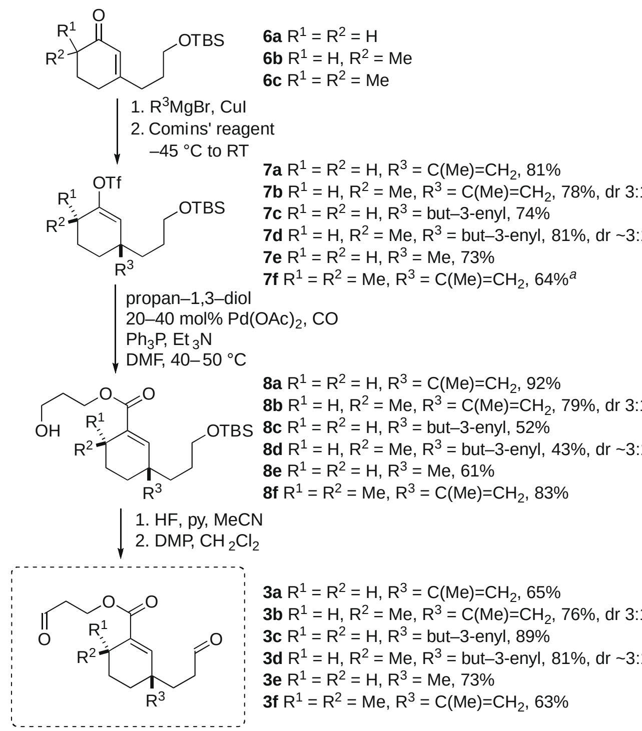
Interestingly, the sequential cyclization of **3f** containing a *gem*-dimethyl group gave **5f** containing the opposite stereochemistry at the quaternary stereocenter constructed during the aldol stage of the cascade (Scheme 6). The structure of **5f** was confirmed by X-ray crystallographic analysis.[14] We had previously observed a similar switch in diastereoselectivity in the protonation of an analogous Sm(III)-enolate.[6] It is likely that this switch is evidence of a different conformation for the intermediate enolate where the most accessible face is now the top face.

The highly diastereoselective cascade reactions begin with an *anti*-selective ketyl-olefin cyclization through transition structure **9** to give samarium enolates **10**.[8] We believe that chelation to Sm(III) leads to selective enolate formation and subsequently to diastereoselective aldol cyclization through six-membered transition structure **11** on the most open bottom face of enolates **10** (Scheme 7). Substrate **3f** is an exception and the aldol cyclization proceeds through attack on the top face of a Sm(III)-enolate in a different conformation (not shown).

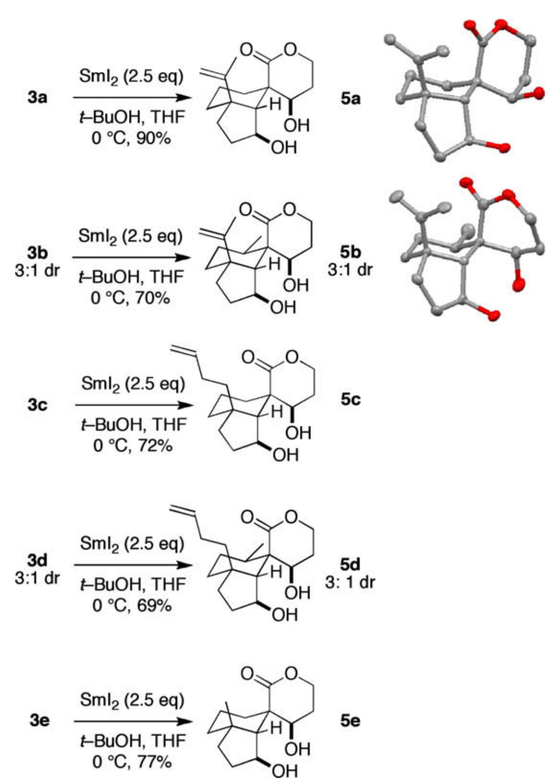
The origin of the selectivity for one aldehyde over the other in our studies, and in the original reduction reported by Takahashi and Nakata,[7] remains unclear. It is thought that the reduction of carbonyl groups with SmI_2 is reversible, with the ketyl radical-anion being drained from the equilibrium by cyclization.[15] As only aldehyde group 1 in **3** is able to undergo facile cyclization, that aldehyde is seen to react in the presence of the other. Alternatively, pre-coordination of samarium to the aldehyde and ester carbonyl



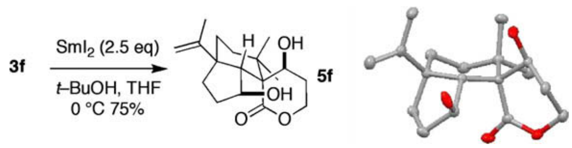
Scheme 3. Proposed sequential dialdehyde cyclizations mediated by SmI_2.



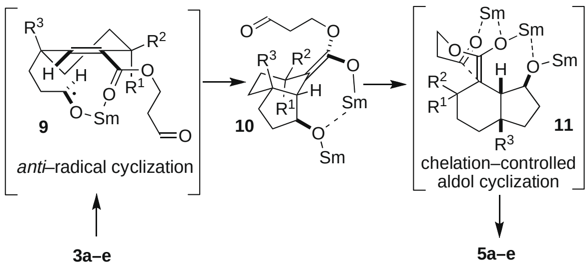
Scheme 4. Synthesis of dialdehyde cyclization substrates **3a**–**f**. [a] **7f** was formed by cuprate addition (82%), followed by triflate formation in a separate step (LDA, Comins' reagent, 78%).



Scheme 5. Sequential dialdehyde cyclizations mediated by SmI_2.



Scheme 6. Sequential dialdehyde cyclization of **3f** mediated by SmI_2.



Scheme 7. Origin of diastereoselectivity in the dialdehyde cyclization sequence.

groups may increase the reactivity of the proximal aldehyde group 1 leading to its selective reduction over the more-remote aldehyde.[8] It is well appreciated that pre-coordination of Lewis acidic samarium to the carbonyl and unsaturated ester components in ketyl-olefin additions is important for promoting reaction and controlling the diastereoselectivity of such additions.[16]

In summary, we have shown the feasibility of SmI_2-mediated, dialdehyde cyclization cascades in which one aldehyde is reduced while the other waits in line. In the dialdehyde cyclization cascades studied here, two rings and four contiguous stereocenters are generated with high diastereocontrol. We believe that the cascade reaction of dialdehydes constitutes a new class of SmI_2-mediated sequence.[1a]

Acknowledgments

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8. When the alkene is sufficiently electron deficient, as is the case with α,β-unsaturated esters, an alternative mechanism involving reduction of the alkene and a subsequent radical or anionic addition to the aldehyde is also possible, although such a mechanism is less frequently proposed. This alternative mechanism could also explain the selectivity seen in our studies and those of Takahashi and Nakata.
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13. No minor diastereoisomers were observed in the crude ^1H NMR. For spirocycle **5a**: SmI_2 in THF (0.1 M, 6.9 mL, 0.690 mmol) was added to degassed *t*-BuOH (1.8 mL) and the resulting solution was stirred under a nitrogen atmosphere for 20 minutes before being cooled to 0 °C (ice bath). After cooling, the dialdehyde **3a** (77 mg, 0.277 mmol) was added dropwise as a solution in THF (2 mL), and the reaction was stirred for 30 min before excess SmI_2 was quenched by allowing air to reach the reaction. Once the solution was yellow, a saturated aqueous solution of K/Na tartrate was added and the crude reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic fractions were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude products were purified by chromatography on silica gel to give spirocycle **5a** (70 mg, 90%, dr >95:5) as a colorless solid. Mp 191 °C (CH_2Cl_2–hexane). ^1H NMR (DMSO-d_6, 400 MHz): δ 1.04–1.18 (2H, m, CH_2), 1.28–1.4 (1H, m, CH_2), 1.41–1.56 (3H, m, CH_2), 1.58–1.69 (1H, m, CH_2), 1.70–1.84 (2H, m, CH_2), 1.76 (3H, s, CH_3), 1.84–1.98 (1H, m, CH_2), 2.01–2.14 (1H, m, CH_2), 2.14–2.28 (1H, m, CH_2), 2.42 (1H, d, *J* = 7.8 Hz, C*H*CHOH), 3.98 (1H, m, CH_2C*H*OH), 4.23 (1H, m, 1H from CH_2O), 4.33 (2H, m, CHC*H*OH and 1H from CH_2O), 4.57 (2H, s, =CH_2), 5.56 (1H, d, *J* = 4.0 Hz, O*H*), 5.75 (1H, d, *J* = 4.3 Hz, O*H*). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.4, 19.9, 25.5, 28.7, 29.7, 31.4, 37.9, 49.2, 49.7, 50.0, 65.0, 71.0, 72.9, 107.2, 150.0, 173.9. ν_{max} (thin film) cm^{-1} 3335 (br), 2924 (s), 2862 (m), 2849 (m), 1715 (s, C=O), 1632 (w), 1451 (w), 1257 (m). MS (EI^+) *m/z* (%): 303 (100, M+Na), 281 (42, M+H). HRMS: calcd for $C_{16}H_{24}O_4Na$ (M+Na): 303.1567. Found: 303.1566.
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