Samarium(II) Iodide Induced Sequential Intramolecular Nucleophilic Acyl Substitution and Stereospecific Intramolecular Meerwein–Ponndorf–Verley Reduction/ Oppenauer Oxidation

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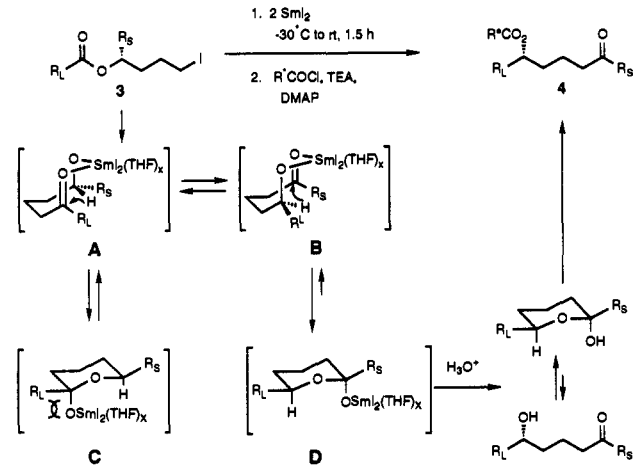
Extensive studies of Meerwein–Ponndorf–Verley (MPV) reductions[1] and complementary Oppenauer oxidations[2] have revealed intimate details of these reactions, including factors leading to the observed thermodynamic equilibria between different carbonyl substrates undergoing the redox process.[3] Unfortunately, little success has been achieved in controlling stereochemistry in the reductive process. Although cases of high relative asymmetric induction have been observed for MPV reductions,[4] there are few reported examples of high diastereotopic face selectivity in intramolecular versions of this reaction.[5] Herein we report our preliminary results describing an unprecedented samarium(II) iodide promoted sequential intramolecular nucleophilic acyl substitution reaction and stereospecific MPV reduction/Oppenauer oxidation reaction[6] in which an unusual thermodynamic driving force provides surprising ratios of hydroxy ketone products, neither the sense nor magnitude of which is precedented.

In conjunction with our discovery that the intramolecular Barbier reaction can proceed by an intermediate organosamarium species,[7] we recently extended our studies to include intramolecular nucleophilic acyl substitution reactions.[8] A substitution pattern in which we were particularly interested is illustrated by the examples in Table I. Samarium(II) iodide promoted cyclization of such substrates was expected to provide ketones with the stereogenic center distal to the carbonyl functionality. As indicated by entry 1 in Table I, cyclization to form the γ-hydroxy ketone proceeded as predicted. However, the δ-hydroxy ketone expected from reaction of the homologous substrate was not formed (entry 2). The single constitutional isomer isolated was formed from initial nucleophilic acyl substitution followed by an MPV/Oppenauer intramolecular redox process. The isopropyl derivative **1c** (entry 3) also exhibited complete intramolecular redox chemistry, with the hydroxyl functionality located adjacent to the sterically more demanding substituent in the final product. Differentiation between a methyl group and an ethyl group (3.5:1) as exhibited in entry 4 further highlights the high selectivity of this process. Substrate **1e** cyclized without intramolecular hydride transfer as expected in light of the results from entry **1b**. Subjection of substrate **1f** to the reaction conditions resulted in a 1:1 mixture of constitutional isomers, further supporting the premises that an equilibrium process is involved and that this equilibrium is controlled exclusively by the steric requirements of the attached alkyl groups.

Scheme I



In traditional MPV/Oppenauer redox processes, the equilibrium favors production of 1° alcohols over 2° alcohols. In fact, only in select, easily reducible ketones can the equilibrium be shifted to any extent.[9] Amazingly, the results in entry 7 demonstrate that the equilibrium in the present case clearly favors the secondary hydroxy aldehyde, an unprecedented result. Obviously, the normal thermodynamic driving forces for these types of reactions have conceded to a second, more energetically significant, equilibrium process.

Scheme I depicts the pertinent processes that we currently support in controlling the observed selectivity of the intramolecular hydride transfer process. The eight-membered-ring samarium(III) chelates **A** and **B** are analogous to transition structures invoked previously in two different studies concerned with diastereoselective SmI_2 promoted reactions.[10] However, although the stereospecificity in the present case can be attributed to this type of templated chelate, the thermodynamic product of the reaction is not decided by intermediates derived directly from these species. Further, the open chain samarium(III) 5-oxidocarbonyl complex seems an unlikely candidate for the observed thermodynamic products of the reaction. Rather, the samarium(III) 2-oxidotetrahydropyrans **C** and **D** appear to be the ultimate product-determining species.[11] Preliminary AMPAC calculations indicate that the open chain hydroxy carbonyl isomers are relatively close in energy (ca. 1-kcal difference favoring the unobserved isomer for the hydroxy ketone of **2b**). However, the same calculations correctly predict the major isomer of the samarium(III) 2-oxidotetrahydropyrans (3–5-kcal difference for **C** and **D** of **2b**).

The final aspect of our investigation addressed the enantioselectivity of this process. Assuming that intramolecular hydride delivery occurred through complexed intermediates **A** and **B** as shown in Scheme I, complete stereospecificity was predicted. Entries 8–10 in Table I support this hypothesis. Additionally, the sense of asymmetric induction was correctly predicted by employing the intermediates depicted in Scheme I.

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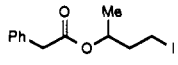
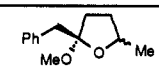
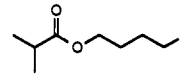
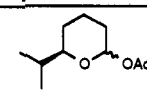
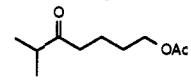
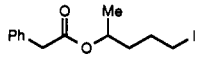
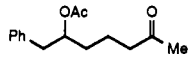
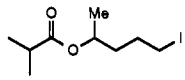
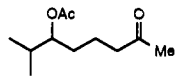
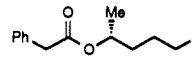
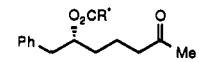
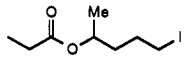
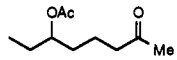
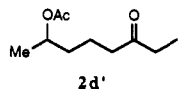
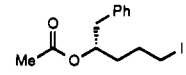
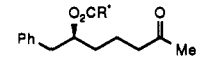
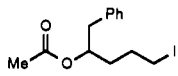
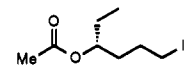
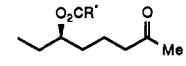
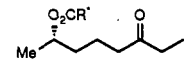
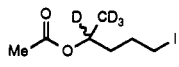
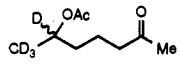
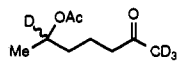
Table I. Samarium(II) Iodide Promoted Sequential Intramolecular Nucleophilic Acyl Substitution and MPV Reduction/Oppenauer Oxidation

entry	substrate	product[a]	isolated yield (%)	entry	substrate	product[a]	isolated yield (%)
1	 1a	 2a	84 [b]	7	 1g	 2g  2g'	83 [e]
2	 1b	 2b	79				
3	 1c	 2c	77	8	 3a	 4a	78 [f,g]
4	 1d	 2d  2d'	83 [c]	9	 3b	 4b	79 [f,h]
5	 1e	2b	81	10	 3c	 4c +  4c'	83 [f,g]
6	 1f	 2f  2f'	82 [d]				

[a] In entry 1 the crude reaction mixture was treated with MeOH and catalytic acid, while in entries 2–7 the crude reaction mixture was treated with Ac_2O, TEA, and DMAP in CH_2Cl_2. The method of workup has no effect on constitutional isomer ratio. [b] Isolated as a 1.5:1 mixture of diastereomers. [c] Isolated as a 3.5:1 mixture of constitutional isomers (**2d**:**2d'**). [d] Isolated as a ca. 1:1 mixture of constitutional isomers. [e] Isolated as an 8:1 mixture of constitutional isomers (**2g**:**2g'**). Compound **2g** was isolated as a 1.5:1 mixture of cis:trans isomers. [f] Products were isolated as the corresponding Mosher ester derivative, and ratios were determined by comparison with racemic material by ^{19}F NMR or ^1H NMR [from (*R*)-Mosher acid chloride]. The stereochemistry of products **4a** and **4b** was determined by comparison to the Mosher ester derivative of (6*S*)-6-hydroxy-7-phenylheptan-2-one prepared enantiomerically enriched by an unambiguous route (see supplementary material). The absolute configurations of the two remaining compounds were assigned by analogy. [g] Both **3a** and **4a** were 87% ee. [h] Both **3b** and **4b** were 93% ee. [i] Isolated as a 3.5:1 mixture of constitutional isomers (**4c**:**4c'**), both of which were 91% ee from **3c** of 91% ee.

This novel sequential process provides a convenient entry to chiral, nonracemic δ-hydroxy ketones, and we are currently optimizing yields and selectivities in continuing investigations of this and related reactions.

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Supplementary Material Available: Complete experimental details and spectral data for all of the reactions described herein, as well as details of structural proofs for the enantiomerically enriched products generated (11 pages). Ordering information is given on any current masthead page.