Samarium(II) Iodide promoted Reductive Fragmentation of γ-Halo Carbonyl Compounds: Application to the Enantiospecific Synthesis of (−)-Oudemansin A

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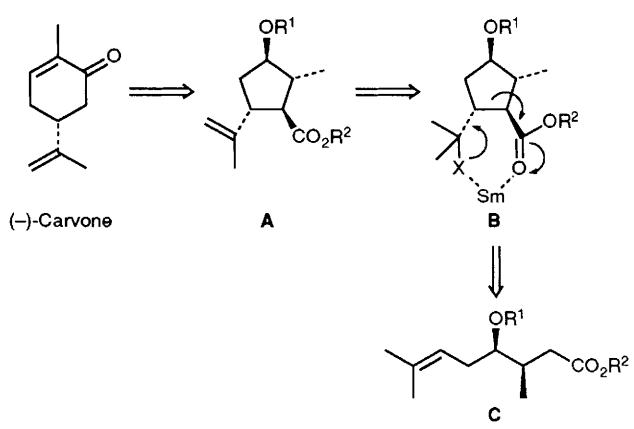
The reductive regioselective bond-cleavage reaction of γ-halo carbonyl compounds with samarium(II) iodide is developed and its utilisation in the enantiospecific synthesis of (−)-oudemansin A is described.

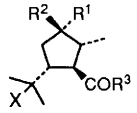
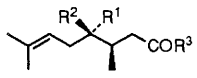
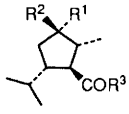
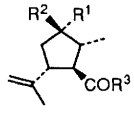
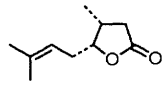
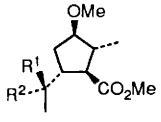
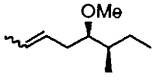
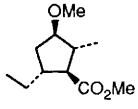
Development of the chemistry of samarium(II) iodide[1] has been of continuing interest in organic synthesis because of its quite unique and useful properties, such as powerful reducing ability in addition to the chemoselectivity. Although various dehalogenations and deoxygenation reactions of α-hydroxy, α-alkoxy, or α-acyloxycarbonyl compounds are widely investigated to date in the variety of useful transformation utilising samarium(II) iodide, little attention has focused on the fragmentation reaction. In 1982, Magnus and his coworkers published[2] a samarium(II) iodide promoted reductive cleavage of a 2-chloroethyl carbamate to the corresponding amine and also a reductive fragmentation reaction of a 11α-steroidal xanthate. This strategy was successully extended to deprotection of a (2,2,2-trichloroethoxy) methyl ether by Evans and Hoveyda.[3] Crombie and Rainbow also reported[4] the reductive 1,2-eliminations of 3-chloro furans and pyrans using samarium(II) iodide to give the corresponding alkenes.

During the course of our studies[5] directed toward the synthesis of physiologically active natural products utilising the cyclopentane derivative **A**, readily accessible from a monoterpene, carvone, as a chiral starting material, we wished to develop an efficient method for the reductive carbon–carbon bond cleavage reaction regioselectively at the β-position to the ester function. Since samarium(II) iodide can interact with both the halogen atom and the carbonyl functional group of γ-halo carbonyl compounds, presumably forming a seven-membered transition state **B**, a concerted fragmentation as depicted in Scheme 1 would reasonably be expected, providing the acyclic alkene **C** with retention of the chiral centres as presented in the starting material, during the dehalogenation reaction. We herein report a samarium(II) iodide promoted bond-cleavage reaction of γ-halo carbonyl compounds and its application to the enantiospecific synthesis of (−)-oudemansin A.



Scheme 1

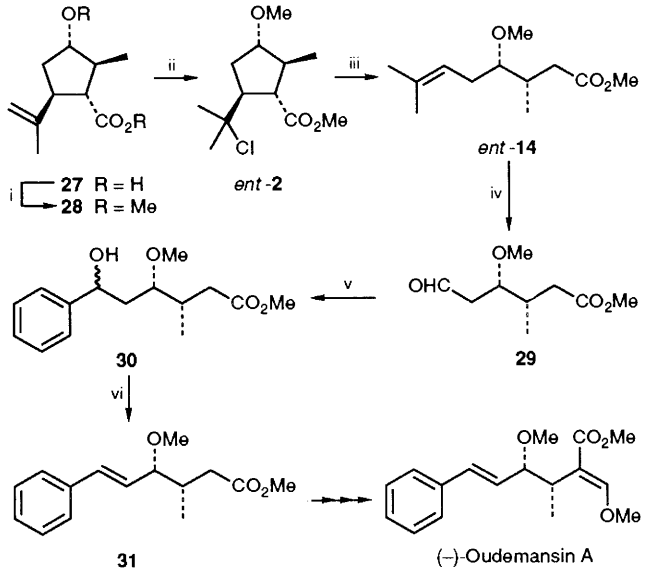
Table 1 SmI_2 promoted fragmentation reaction of γ-halo carbonyl compounds

Starting material	Product yield (%)			
				
		R^1 = H, R^2 = OMe, R^3 = OMe		
1; R^1 = H, R^2 = OMe, R^3 = OMe, X = Br	**14** (48%)	**15** (17%)	**16** (14%)	—
2; R^1 = H, R^2 = OMe, R^3 = OMe, X = Cl	**14** (77%)	—	—	—
		R^1 = H, R^2 = OH, R^3 = OMe		
3; R^1 = H, R^2 = OH, R^3 = OMe, X = Br	—	**18** (39%)	**19** (17%)	**17** (15%)
4; R^1 = H, R^2 = OH, R^3 = OMe, X = Cl	—	**18** (37%)	—	**17** (24%)
		R^1 = H, R^2 = OTBS, R^3 = OMe		
5; R^1 = H, R^2 = OTBS, R^3 = OMe, X = Br	**20** (55%)	**21** (17%)	**22** (10%)	—
6; R^1 = H, R^2 = OTBS, R^3 = OMe, X = Cl	**20** (78%)	—	—	—
		R^1 = OTBS, R^2 = H, R^3 = OMe		
7; R^1 = OTBS, R^2 = H, R^3 = OMe, X = Cl	**23** (60%)	—	—	—
		R^1 = H, R^2 = OMe, R^3 = Me		
8; R^1 = H, R^2 = OMe, R^3 = Me, X = Br	**24** (43%)	—	—	—
9; R^1 = H, R^2 = OMe, R^3 = Me, X = Cl	**24** (18%)	—	—	—
				
	25	**26**		
10; R^1 = H, R^2 = Cl	**25** (21%)	**26** (17%)		
11; R^1 = Cl, R^2 = H	**25** (29%)	**26** (12%)		
12; R^1 = H, R^2 = Br	**25** (64%)	—		
13, R^1 = Br, R^2 = H	**25** (66%)	—		

Thus, the γ-bromo ester **1**, prepared from the cyclopentane **16** by addition of hydrogen bromide in acetic acid, was treated with 2.5–4.0 equimolar amounts of samarium(II) iodide in tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA)[6] (20:1, v/v) at ambient temperature to afford the desired alkene **14** in 48% yield (runs 1 and 5).† When this reaction was carried out in the absence of hexamethylphosphoric triamide as a cosolvent, reductive dehalogenation only occurred providing the ester **15** in good yield. Reaction of the γ-chloro compound **2**, derived from **16** by treatment with hydrogen chloride in diethyl ether, with samarium(II) iodide under the same reaction conditions as above provided **14** in 77% yield (Table 1, entries 2, 6 and 7). Treatment of the γ-chloro compound **2** with tri-n-butyltin hydride and azoisobutyronitrile in refluxing benzene under a radical initiating reaction condition gave none of the fragmentation product, but the dehalogenated compound **16**. Reduction of **2** with zinc powder in acetic acid also failed to provide the desired product. Similar reactions for the hydroxy derivatives **3** and **4** induced a lactonisation affording the γ-lactone **17** (entries 3 and 4). Although it is premature to present a detailed mechanistic rationale for the observed fragmentation reaction, these results suggest that this reaction would occur *via* a two-electron reduction process involving further reduction of the initially generated radical prior to either proton abstraction of a radical-induced fragmentation. This fragmentation was also effective to the secondary γ-halo esters **10**–**13** where the stereoselectivity could not be observed providing a mixture of the alkenic isomers **25** in the same ratio ($E:Z$ = 3:2 or *vice versa*) (runs 10–13). Results obtained are summarised in Table 1. Interestingly, reaction of γ-halo ketone with samarium(II) iodide under similar reaction conditions as above, usually furnishing a cyclobutanol derivative *via* a ketyl radical,[7] afforded the bond cleaved product, probably owing to the biased structure inherent in a *trans*-bicyclo[3.2.0]heptane ring system (entries 8 and 9).

The fragmentation reaction developed above was applied to the enantiospecific synthesis of the antifungal metabolite, (−)-oudemansin A, isolated from mycelial cultures of *Oudemansiella mucida*.[8] This antibiotic has been known[9] to inhibit eukaryotic respiration by blocking cytochrome b-c_1 electron transfer.

† The standard experimental procedure is as follows: To a stirred solution of γ-halo carbonyl compound (0.1 mmol) in dry THF (0.5 cm^3) in the presence of molecular sieves 4 Å under argon was added a solution of SmI_2 (2.5–4.0 equiv.) in dry THF–HMPA (10 cm^3, 20:1 v/v) at ambient temperature over the period of 1 h. After stirring for 5 min, the mixture was treated with saturated aqueous sodium hydrogen carbonate and the whole mixture was diluted with diethyl ether. The ethereal layer was washed with water, dried (Na_2SO_4), and concentrated to leave a residue, which was purified by column chromatography on silica gel.



Scheme 2 *Reagents and conditions*: i, NaH, MeI, DMF, room temp.; ii, HCl(gas), Et_2O, room temp.; iii, SmI_2, THF–HMPA, room temp.; iv, O_3, CH_2Cl_2, −78 °C then Me_2S; v, PhMgBr, THF, −78 °C; vi $(MeSO_2)_2O$, DMAP, benzene, reflux

The hydroxy acid **27**[5] derived from (+)-carvone, was methylated with methyl iodide in the presence of sodium hydride (60% dispersion in mineral oil) in *N,N*-dimethylformamide to give the methyl ether **28**, which on treatment with hydrogen chloride in ether provided the γ-chloro ester *ent*-**2** in 84% yield from **27**. Samarium(II) iodide promoted carbon–carbon bond cleavage reaction of *ent*-**2** in tetrahydrofuran–hexamethylphosphoric triamide at ambient temperature afforded the acyclic alkene *ent*-**14**, which was then converted into the aldehyde **29** by ozonolysis in a usual manner, in 70% yield. Reaction of **29** with phenylmagnesium bromide, followed by treatment of the resulting alcohol **30** with methanesulfonic anhydride in refluxing benzene in the presence of 4-dimethylaminopyridine (DMAP) gave the alkene **31**, {$[\alpha]_D$ −11.5 (c 0.24, CH_2Cl_2), lit.,[10] $[\alpha]_D$ −11.9 (*c* 1.55, CH_2Cl_2)}, in 54% yield from **29**, spectroscopic data including the specific optical rotation were identical to those reported.[10] Since the ester **31** was already converted into (−)-oudemansin A,[10,11] the present result constitutes its formal synthesis.

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