Scope and Limitations of Samarium Diiodide Induced Cyclizations of Alkenyl-Substituted γ-Keto Esters to Benzannulated Cyclooctanol Derivatives

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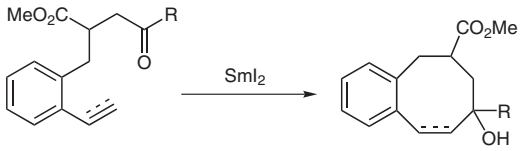
Received 9 April 2009

Abstract: A series of γ-keto esters bearing various alkenyl substituents were synthesized and subjected to samarium diiodide mediated 8-*endo-trig* ketyl–alkene coupling reactions. Highly substituted benzannulated cyclooctanol derivatives were obtained in good yields and with moderate to excellent stereoselectivities. The obtained results demonstrate the influence of steric and electronic factors on the regio- and stereoselectivity of ketyl-alkene cyclizations. Stilbenyl-substituted derivatives can cyclize either to cyclooctanol or to cycloheptanol derivatives depending on the substitution pattern at the carbonyl group.

Key words: samarium diiodide, ketyl, cyclizations, radical reactions, medium-sized rings, cyclooctanols, cycloheptanols

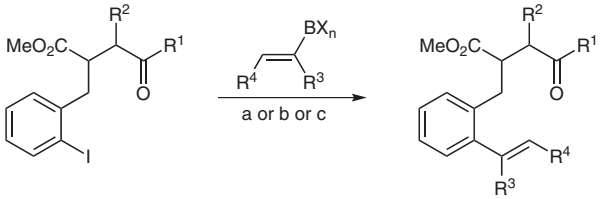
Medium-sized rings, in particular cyclooctane derivatives, are important structural features in a variety of natural products and biologically active substances. The development of new efficient methods for their construction is therefore highly desirable.[1] Since 1977 samarium diiodide is known as a selective electron-transfer reagent for many synthetic transformation,[2] and it often allows regio- and stereoselective construction of ring systems under mild reaction conditions.[3] SmI_2 has been reported to successfully promote the formation of medium-sized rings in a number of ways. Direct cyclization strategies used SmI_2 to induce, for example, intramolecular coupling reactions of α-bromoesters with aldehydes,[4a] allyl chlorides with aldehydes[4b] and ketones,[4c] as well as ketones with alkenes.[4d] Indirect methods employed SmI_2 in sequential reactions, generating intermediates which then formed the desired ring either via intramolecular SmI_2-induced acyl substitution[5a–5d] or by fragmentation reactions.[5e]



Scheme 1 Samarium diiodide induced cyclizations of γ-styryl- and γ-phenylalkynyl-substituted ketones to benzannulated cyclooctanols

Our group has utilized SmI_2 for cyclizations of a variety of γ-styryl- and γ-phenylalkynyl-substituted ketones leading to benzannulated cyclooctanol[6a,b,3b] and cyclooctenol[6c,3b] derivatives, respectively (Scheme 1). In continuation of this work we have now extended our methodology to the cyclization of precursors with additional substituents at the alkene moiety. Herein we describe how steric and electronic factors at the alkene moiety influence the regio- and the stereoselectivity of the samarium-ketyl cyclizations.

The preparation of starting materials was performed analogously to our previously described modular approach[6a,b] via siloxycyclopropanes,[7] which allowed simple syntheses of γ-keto esters **1**–**4** bearing a 2-iodobenzyl moiety (Scheme 2). These were then equipped with different alkenyl groups using Suzuki coupling reactions[8a–8d] to furnish the cyclization precursors **5**–**13**.



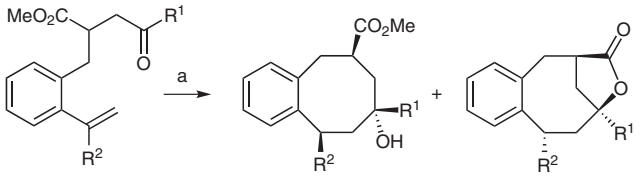
1	R^1 = Me	R^2 = H	89%[a]	R^3 = Me	R^4 = H	**5**
			93%[b]	R^3 = H	R^4 = Me	**6**
2	R^1 = Et	R^2 = H	91%[b]	R^3 = H	R^4 = Me	**7**
3	R^1 = *i*-Pr	R^2 = H	75%[a]	R^3 = Me	R^4 = H	**8**
			87%[b]	R^3 = Ph	R^4 = H	**9**
			88%[b]	R^3 = H	R^4 = Me	**10**
			90%[c]	R^3 = H	R^4 = *c*-Pr	**11**
			99%[b]	R^3 = H	R^4 = Ph	**12**
4	$R^1 = R^2 = -(CH_2)_4-$		95%[b]	R^3 = H	R^4 = Ph	**13**
	(dr = 1:1)					(dr = 1:1)

Scheme 2 Synthesis of cyclization precursors **5**–**13**. *Reagents and conditions*: a) for coupling of alkenyl trifluoroborates: $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), Cs_2CO_3 (3 equiv), THF–H_2O (10:1, 4 mL/mmol), 70 °C, 4 h; b) for coupling of alkenyl boronic acids: $Pd(OAc)_2$ (5 mol%), Ph_3P (20 mol%), K_2CO_3 (1.5 equiv), DMF (4 mL/mmol), 70 °C, 12–72 h; c) for coupling of alkenyl boronic esters: $Pd(Ph_3P)_2Cl_2$ (3 mol%), dppf (3 mol%), K_2CO_3 (3 equiv), DMF (4 mL/mmol), 80 °C, 18 h.

We have then systematically investigated these starting materials in samarium diiodide induced intramolecular ketyl–alkene coupling reactions. The samarium diiodide induced reactions of 2-propenyl-substituted γ-keto esters **5** and **8** under standard conditions (2.2 equiv SmI_2, 18 equiv HMPA, 2.0 equiv *t*-BuOH in THF) furnished mixtures of **14** and **15**,[9] respectively, **16** and **17** in good combined yield and with low to moderate stereoselectivity in favor of products with *trans* arrangement of the methoxycarbonyl and the hydroxyl group[10] (Scheme 3). The stereo-

SYNLETT 2009, No. 13, pp 2089–2092
Advanced online publication: 01.07.2009
DOI: 10.1055/s-0029-1217520; Art ID: G12209ST

selectivity was slightly improved for substrate **8** with a larger substituent R^1 adjacent to the carbonyl group. Analogous γ-keto ester precursors bearing a styryl substituent underwent this cyclization with slightly higher stereoselectivity, also in favor of *trans* products.[6b] On the other hand, the cyclization of compound **9**, equipped with a phenyl substituent at the α-styryl position, afforded two epimeric γ-lactones (*cis* products) **18a** and **18b**[11] in a ratio of 1.7:1.

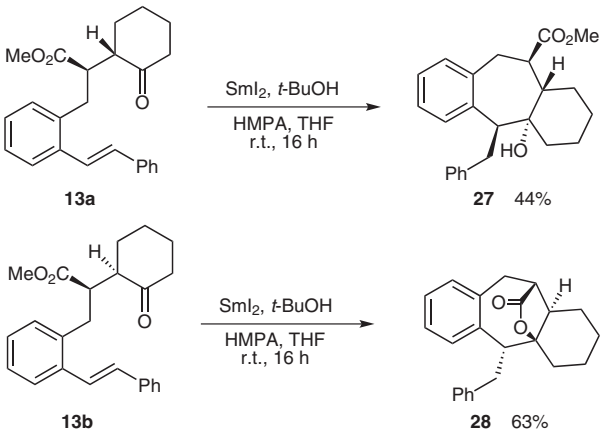


5	R^1 = Me	R^2 = Me	**14** 40%	**15** 38%
8	R^1 = *i*-Pr	R^2 = Me	**16** 54%	**17** 28%
9	R^1 = *i*-Pr	R^2 = Ph	--	**18** 59%[b]

Scheme 3 Samarium diiodide induced 8-*endo-trig* cyclizations of starting materials **5**, **8**, and **9** substituted at the α-styryl position. a) *Reagents and conditions*: SmI_2 (2.2 equiv, 0.1 M in THF), HMPA (18 equiv), *t*-BuOH (2.0 equiv), THF (40 mL/mmol), r.t., 16 h. b) Isolated as two diastereomers with respect to the R^2-substituted stereogenic center (dr = 1.7:1).

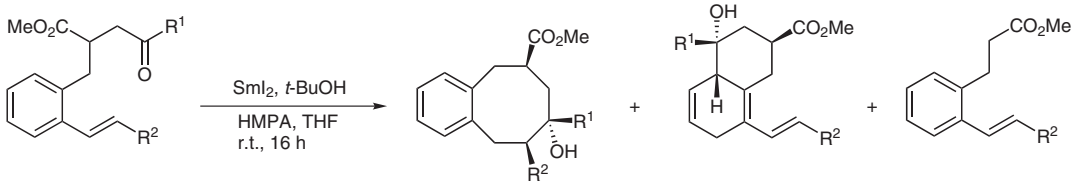
Subsequently, we have studied the samarium diiodide induced cyclizations of γ-keto esters **6**, **7**, and **10**–**12** bearing the substituents at the β-styryl position (Scheme 4). In this series of substrates *trans*-substituted products were formed in good yields and with excellent stereoselectivities. However, in several cases side products were formed. Methyl ketone **6** provided the expected cyclization product **19** but it also gave significant amounts of ketyl–aryl coupling[12] product **20**. The ketyl–aryl coupling was not observed in the cyclizations of the γ-keto esters bearing larger substituents adjacent to the carbonyl group. Substrates **7** and **10** afforded *trans*-cyclooctanol derivatives **21** and **23** in a remarkably clean fashion. However, if the steric hindrance at the reacting centers is too high, for example, in the case of γ-keto ester **11** bearing branched substituents both at the carbonyl and the alkene moieties, the reaction afforded fragmentation product **25** as major component along with only moderate quantities of the desired cyclooctanol derivative **24**. The stilbenyl-substituted γ-keto ester **12** afforded the cyclooctanol derivative **26** in good yield, taking into account the reisolated starting material. It should be emphasized here that the 1,2-diaryl alkene unit could potentially react with samarium-ketyls at both carbon atoms, affording alternative stabilized benzylic radicals. Interestingly, the 8-*endo-trig*-cyclization mode was clearly preferred here over the 7-*exo-trig* reaction.

Finally, the reactions of two epimers of the stilbenyl-substituted cyclic γ-keto ester **13** were investigated (Scheme 5). In our previous report cyclizations of the analogous styryl-substituted keto esters were described.[6b] Interestingly, only the unlike-configured starting material underwent the cyclization process while the like-configured starting material was inert to reaction conditions due to its impaired geometry for cyclization. To our surprise both stilbenyl-substituted precursors **13** afforded cyclization products, and in both cases formation of cycloheptanol derivatives was preferred. Remarkably, the like-configured **13b**, which was expected to be unreactive, gave the tetracyclic product **28**[11] in better yield than its epimer **13a** furnishing compound **27**. Studies to determine scope and selectivity of the formation of similar cycloheptanol derivatives via samarium diiodide mediated processes are currently under way.



Scheme 5 Samarium diiodide induced *7-exo-trig* cyclizations of stilbenyl-substituted γ-keto esters **13a** and **13b**

Models explaining the observed stereoselectivities are so far fairly speculative, in particular with respect to the stereogenic center formed by the final protonation step (compounds **14**–**18** as presented in Scheme 3). A transition state for the 8-*endo-trig* cyclization of γ-keto esters sub-



6	R^1 = Me	R^2 = Me	**19** 54%	**20** 20%	--
7	R^1 = Et	R^2 = Me	**21** 56%	--	**22** 5%
10	R^1 = *i*-Pr	R^2 = Me	**23** 63%	--	--
11	R^1 = *i*-Pr	R^2 = *c*-Pr[a]	**24** 24%	--	**25** 47%
12	R^1 = *i*-Pr	R^2 = Ph	**26** 47%[b]	--	--

Scheme 4 Samarium diiodide induced 8-*endo-trig* cyclizations of precursors **6**, **7**, **10**–**12** substituted at the β-styryl position; a) *c*-Pr = cyclopropyl; b) 20% of the starting material was reisolated from the reaction mixture.

stituted at the β-styryl position is suggested in Figure 1 which may rationalize our results depicted in Scheme 4. The methoxycarbonyl group and the substituent R^1 occupy pseudoequatorial positions, while the bulky samarium(III)oxy substituent is forced into a pseudoaxial position. The olefin approaches in an antiperiplanar fashion to the samarium(III)oxy group[13] leading to a staggered conformation. As a consequence *trans* products are obtained selectively, in which the R^2 group is situated at the same face of the eight-membered ring as the methoxycarbonyl and the R^1 substituent. More detailed studies are required to substantiate these ideas.

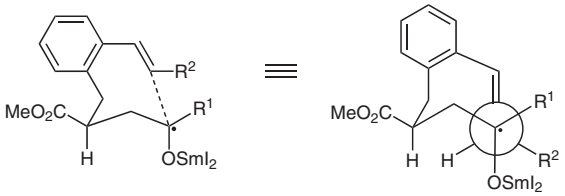


Figure 1 Suggested transition state for 8-*endo-trig* cyclizations of γ-keto esters substituted at the β-styryl position leading to *trans* products with high selectivity (HMPA ligands at samarium are omitted for simplicity).

In conclusion, we have extended our approach to cyclooctanol derivatives to substrates bearing substituents at the alkene moiety. We have successfully determined how the newly introduced substituents influence regio- and stereoselectivity of an intramolecular 8-*endo-trig* ketyl–alkene coupling reaction. Furthermore, the formation of interesting tricyclic and tetracyclic products by 7-*exo-trig* cyclization was observed.

Acknowledgment

Generous support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG is most gratefully acknowledged.

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(9) **Typical Procedure for SmI_2-Induced Cyclizations – Conversion of 5 into 14 and 15**
Samarium metal (278 mg, 1.85 mmol) and 1,2-diiodoethane (477 mg, 1.69 mmol) were placed under a flow of argon in a flame-dried, two-necked round-bottomed flask containing a magnetic stirring bar and a septum inlet. THF (20 mL) was added, and the mixture was vigorously stirred at r.t. for 2 h. HMPA (2.40 mL, 13.8 mmol) was added to this solution of SmI_2, and after 10 min of stirring a solution of substrate **5** (200 mg, 0.77 mmol) and *t*-BuOH (146 μL, 1.54 mmol) in THF (31 mL) was added over 2 h. The mixture was stirred at r.t. for 16 h and quenched with sat. aq $NaHCO_3$ solution (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and dried (Na_2SO_4). The products were purified by column chromatography (silica gel, hexane–EtOAc = 10:1) to furnish 80 mg (40%) **14** as colorless oil and 67 mg (38%) **15** as colorless crystals (mp 130–132 °C).
Analytical Data for Methyl (6*RS*,8*RS*,10*RS*)-8-Hydroxy-8,10-dimethyl-5,6,7,8,9,10-hexahydrobenzo[8]-annulene-6-carboxylate (14)
Compound **14** shows temperature-dependent NMR spectra. At r.t. some signals appear broad, measurement at 55 °C allowed to see the signals more clearly. ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ = 1.20 (s, 3 H, 8-Me), 1.33 (dd, *J* = 11.5, 14.7 Hz, 1 H, 7-H), 1.33 (d, *J* = 7.1 Hz, 3 H, 10-Me), 1.62 (dd, *J* = 11.4, 14.3 Hz, 1 H, 9-H), 1.67 (dd, *J* = 3.8, 14.7 Hz, 1 H, 7-H), 1.79–1.83 (m, 1 H, 9-H), 3.10 (dddd, *J* = 2.9, 3.8, 7.5, 11.5 Hz, 1 H, 6-H), 3.16 (dd, *J* = 2.9, 13.9 Hz, 1 H, 5-H), 3.36–3.43 (m, 1 H, 10-H), 3.43 (dd, *J* = 7.5, 13.9 Hz, 1 H, 5-H), 3.68 (s, 3 H, CO_2Me), 6.97–6.99, 7.06–7.10, 7.17–7.25 (3 m, 1 H, 1 H, 2 H, Ar) ppm. The signal for the OH group could not be assigned unambiguously. ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ = 23.2 (q, 10-Me), 30.2 (d, C-10), 32.3 (t, C-5), 36.0 (q, 8-Me), 36.5 (t, C-7), 42.2 (d, C-6), 55.1 (t, C-9), 71.5 (s, C-8), 125.1, 125.9, 127.1, 129.6, 136.5, 146.3 (4 d, 2 s, Ar), 51.7, 176.1 (q, s, CO_2Me) ppm. IR (neat): ν = 3500 (br, OH), 3100-2840 (=CH, CH), 1715 (C=O) cm^{-1}. ESI-TOF: *m/z* calcd for: 217.1255 $[M + H]^+$, 239.1074 $[M + Na]^+$, 255.0813 $[M + K]^+$; found: 217.1267, 239.1095, 255.0844.

Analytical Data for (2*RS*,5*SR*,7*SR*)-5,7-Dimethyl-1,5,6,7-tetrahydro-2,5-methano-4-benzoxonin-3 (2*H*)-one (15)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.9 Hz, 3 H, 7-Me), 1.36 (s, 3 H, 5-Me), 1.43 (dd, *J* = 1.1, 13.9 Hz,1 H, 12-H), 1.55 (dd, *J* = 11.3, 14.6 Hz, 1 H, 6-H), 1.74–1.79 (m, 1 H, 12-H), 2.05–2.09 (m, 1 H, 6-H), 2.76 (dqd, *J* = 1.3, 6.9, 11.3 Hz, 1 H, 7-H), 3.15 (dddd, *J* = 1.1, 2.5, 10.3, 12.8 Hz, 1 H, 2-H), 3.20 (dd, *J* = 12.8, 14.5 Hz, 1 H, 1-H), 3.31 (dd, *J* = 2.5, 14.5 Hz, 1 H, 1-H), 7.00–7.02, 7.15–7.18, 7.28–7.36 (3 m, 1 H, 1 H, 2 H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5 (q, 7-Me), 29.6 (q, 5-Me), 30.0 (d, C-7), 34.2 (t, C-12), 34.5 (t, C-1), 39.3 (d, C-2), 51.4 (t, C-6), 86.3 (s, C-5), 125.4, 126.7, 127.9, 130.4, 136.8, 146.2 (4 d, 2 s, Ar), 181.5 (s, C-3) ppm. IR (KBr): ν = 3065–2825 (=CH, CH), 1755 (C=O) cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_2$ (230.3): C, 78.23; H, 7.88. Found: C, 78.49; H, 7.93.

(10) In *cis* products the lactone bridge is formed under the reaction conditions due to the proximity of the hydroxy and methoxycarbonyl groups.

(11) The relative configurations of the **18b** and **28** were unambiguously determined by the X-ray crystallography (Brüdgam, I.; Lentz, D. *unpublished results*, Freie Universität Berlin). For all other cyclization products the suggested relative configuratations are strongly supported by NOESY correlations.

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