A Novel Sm(II)-Induced Route to Highly Substituted Benzannulated Cyclooctanol Derivatives

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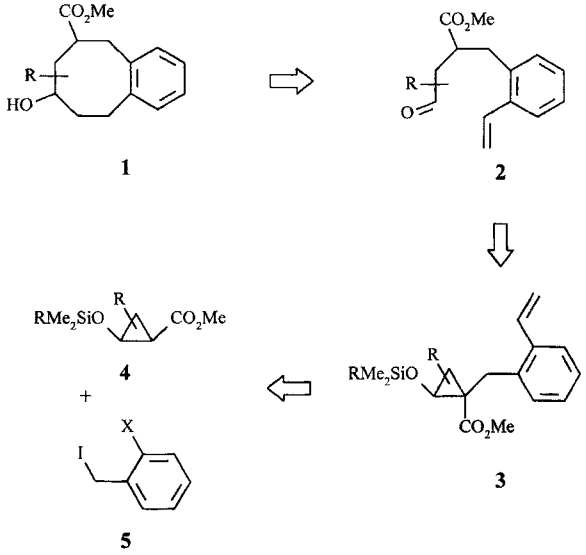
Dedicated to Prof. Peter Welzel on the occasion of his 60th birthday

Abstract: Siloxycyclopropane derivatives **3** with a suitable styrene side chain can effectively be ring opened to precursors **2** which undergo reductive ring closure with SmI_2 to furnish benzannulated cyclooctanols **1** or lactones **7** derived thereof. Tricyclic lactone **7c** can be further substituted by conversion into a brigdehead enolate and reactions with electrophiles.

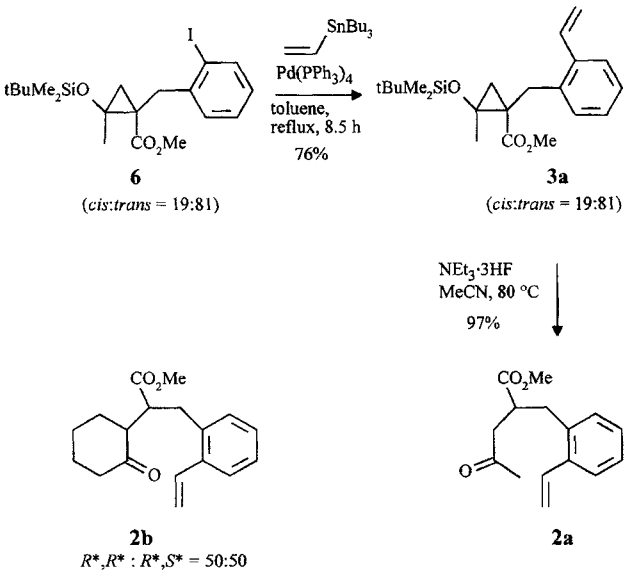
The synthesis of eight-membered rings[1] has attracted considerable efforts during the last years, mainly due to the occurrence of this ring size in taxane diterpenes and other structurally interesting natural products.[2] In this paper we want to present our approach to this challenge with a samarium(II)-induced reductive coupling[3] as the crucial step forming the desired benzannulated cyclooctanol derivatives **1**. Our retrosynthetic analysis reveals that the precursors **2** are to be generated from suitably substituted methyl 2-siloxycyclopropanecarboxylates **3**[4] which may be constructed by combination of the parent cyclopropanes **4** and a benzyl iodide **5** either already bearing the required vinyl substituent (X = $CH{=}CH_2$) or functionalized to allow easy installation of this group (X = I). Thus, our overall strategy to prepare the benzannulated cyclooctanes combines the C_3 fragment **4** with a suitable C_5 building block.



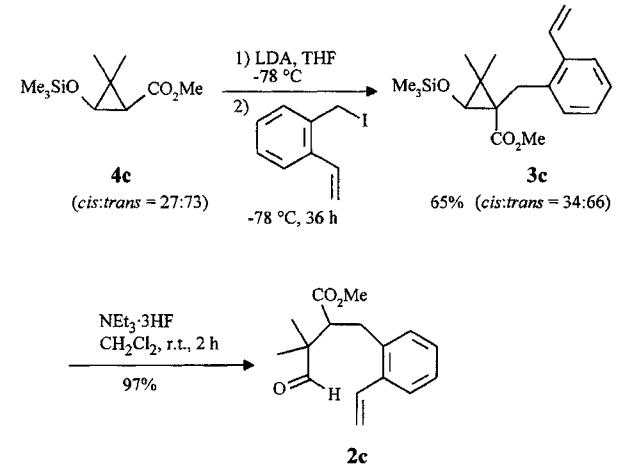
Scheme 1

There are two routes to synthesize the required cyclopropanes **3**. For example, **3a** was obtained by Stille coupling[5] of precursor **6**[6] with tributylvinyltin in satisfying yield. Ring cleavage[7] with $NEt_3{\cdot}3HF$ gave precursor **2a** almost quantitatively. Ketoester **2b** was similarly prepared and obtained as a 1:1 mixture of diastereomers which may be separated by flash chromatography.

The alternative approach introduces the complete C_5 building block. Thus, alkylation[8] of siloxycyclopropane **4c** with *o*-vinylbenzyl iodide[9] produces pentasubstituted cyclopropane derivative **3c** as mixture of diastereomers which was converted into **2c** in excellent yield.



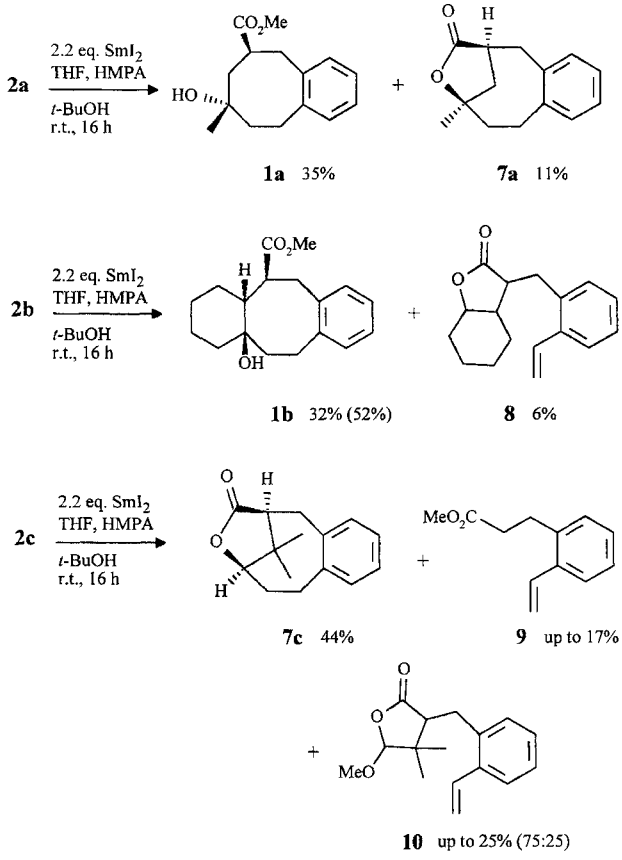
Scheme 2



Scheme 3

The reductive coupling of **2a** was performed with 2.2 equivalents of SmI_2 which was generated by treatment of Sm metal with 1,2-diiodoethane. For efficient coupling the presence of the cosolvent HMPA and the proton source *t*-BuOH was required.[10] Thus, coupling of **2a** provided the desired cyclooctanol derivative **1a** together with the tricyclic lactone **7a** which arises from the diastereomer of **1a** with *cis*-located functional groups. Likewise, one of the diastereomers of **2b** could be converted into tricyclic compound **1b**[11] in rather moderate yield. Taking into account recovered starting material the yield was 52%. The side product **8**, where only reduction of the carbonyl group occurred, demonstrates that ring closure seems to be less favourable in this example. The relative configuration of **1b** was deduced by inspection of models.[12] Only the (*R**,*S**)-diastereomer of **2b** can adopt

the conformation required for cyclization without severe steric repulsion. These considerations lead to the prediction that the six- and eight-membered ring are *cis*-annulated.

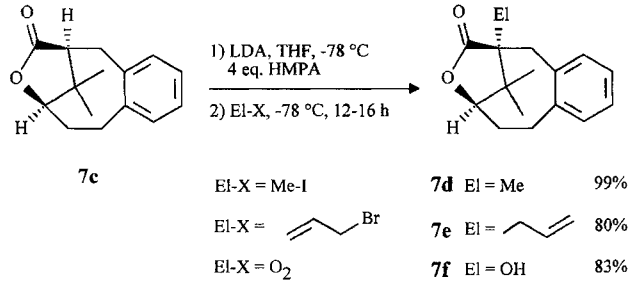


Scheme 4

Finally, precursor **2c** was treated under standard conditions[13] to give the tricyclic compound **7c** in 44% yield[14] together with a fragmentation product **9** and acetal **10**.[15] Taking into account that formation of eight-membered rings is very often unfavourable, the moderate yields of the coupling products **1a/7a**, **1b** and **7c** are quite satisfying. The new method opens a route to highly substituted benzannulated cyclooctanol derivatives - even with high diastereoselectivity in some cases.

However, it must be admitted that ketoesters related to precursor **2a**, but bearing a phenyl or an alkenyl group instead of the methyl substituent, do not undergo the reductive cyclization.[16] Mainly starting material was reisolated after treatment of these compounds with Sm(II).

Due to the geminal dimethyl groups of **7c** the chemistry of this tricyclic lactone attracted our special attention. We tried to introduce further substituents at the bridgehead position by deprotonation/ alkylation. Fortunately, this turned out to be a smooth process for reactive alkyl halides. Alkylation of the bridgehead enolate (generated by LDA treatment of **7c**) with methyl iodide and allyl bromide afforded pentasubstituted lactones **7d** and **7e** in very good yields. Probably due to the severe steric hindrance, reactions of the enolate with less reactive alkyl halides proceeded less satisfactory. However, in these experiments small amounts of alcohol **7f** could be isolated. The suspicion that traces of oxygen were responsible for formation of **7f** was nicely confirmed by deliberate reaction of the enolate with oxygen[17] which furnished the interesting hydroxy-substituted lactone **7f** in good yield.



Scheme 5

In conclusion, we could demonstrate that the novel reductive coupling of suitably substituted styrene derivatives **2** can lead to highly substituted benzannulated cyclooctanol derivatives. The particularly interesting tricyclic lactone **7c** can be further transformed by deprotonation to a bridgehead enolate and reactions with electrophiles. Attempts to incorporate further functional groups into the eight-membered and the benzene ring as well as efforts to convert the lactone into ring A of the taxane skeleton will be reported in due course.

Acknowledgement: Generous support of this work by the Volkswagen-Stiftung, the Fonds der Chemischen Industrie, and the Alexander-von-Humboldt-Stiftung (fellowship for Faiz A. Khan) is most gratefully appreciated. We thank Dr. Margit Gruner for measurements and interpretations of 2D-NMR spectra.

References and Notes

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3) a) Reviews: Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. - Skrydstrop, T. *Angew. Chem.* **1997**, *109*, 355; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 344. - Khan, F. A.; Zimmer, R. *J. Prakt. Chem.* **1997**, *339*, 101. - b) Synthesis of 8-membered rings promoted by Sm(II): Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. - Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705.

4) Review: Reissig , H.-U. *Top Curr. Chem.* **1988**, *144*, 73.

5) Review: Stille, J. K. *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

6) Khan, F. A.; Czerwonka, R.; Reissig, H.-U. *Synlett* **1996**, 533.

7) For a general procedure for ring cleavage of related systems, see: Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802.

8) For a typical alkylation procedure, see: Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 531.

9) This compound is easily available in four steps starting from phthalide.

10) These conditions are similar to those employed by Molander and McKie for the synthesis of less functionalized cyclooctanols (see ref. 3b).

11) The diastereomers have been used either as 1:1 mixture or as separated pure compounds.

12) The NMR data of **1b** are so far not conclusive since the other diastereomers are not available for comparison.

13) **Typical procedure 2c → 7c**: Samarium metal (1.75 g, 11.7 mmol) was added under a flow of Ar to a flame-dried two necked rond-bottomed flask containing a stirring bar and a septum inlet. The flask and the Sm were flame dried. To the Sm was added dry THF (73 ml) followed by 1,2-diiodoethane (3.04 g, 10.8 mmol) and the mixture was stirred for 1.5 h at room temperature. To the resulting deep blue solution of SmI_2 was added dry HMPA (15.6 g, 87.2 mmol) and Ar was bubbled through the mixture for 10 min. Then a solution of aldehyde **2c** (1.17 g, 4.50 mmol) and *t*-BuOH (0.73 g, 9.85 mmol) in THF (208 ml) was added over 2 h and the mixture was stirred for 6 h at room temperature. The solution was quenched with saturated aqueous $NaHCO_3$ solution (50 ml), the layers separated and the aqueous layer was extracted with ether (3x50 ml). The combined organic layer was washed with water, brine and then dried ($MgSO_4$). The resulting crude product (1.12 g) was purified by colum chromatography (neutral alumina, hexane:ethyl acetate = 9:1) to give 144 mg of **9** (17%) and 454 mg of **7c** (44%), which is a colourless solid (m.p. 115-116 °C). - Analytical data of **7c**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.25-7.08 (m, 4H, Ar), 4.27 (t, *J* = 3.5 Hz, 1H, 4-H), 3.20 (dd, *J* = 2.2, 14.8 Hz, 1H, 1-H), 3.08 (dd, *J* = 9.5, 14.8 Hz, 1H, 1-H), 2.98 (dt, *J* = 3.8, 13.5 Hz, 1H, 6-H), 2.71-2.60 (m, 2H, 2-H, 6-H), 2.37-2.19 (m, 1H, 5-H), 2.02 (qd, *J* = 4.0, 15.2 Hz, 1H, 5-H), 1.31, 1.20 (br s, s, 6H, 3-Me, 3-Me). - ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.3 (s, C=O), 139.9, 136.6, 132.1, 129.4, 127.7, 126.5 (2s, 4d, Ar), 88.6 (d, C-4), 52.1 (d, C-2), 41.8 (s, C-3), 33.1 (t, C-5), 31.2 (t, C-1), 29.8 (t, C-6), 33.3, 18.0 (2q, 3-Me, 3-Me). - IR (neat.): ν = 3100-2850 (C-H), 1765 (C=O), 1175, 1140, 1015, 985, 760 cm^{-1}. - $C_{15}H_{18}O_2$ (230.3): calcd. C 78.23, H 7.88; found C 78.62, H 8.27.

14) The structure of **7c** was unequivocally confirmed by an x-ray analysis: Khan, F. A.; Zimmer, R.; Reissig, H.-U. Zahn, G. *Z. Kristallogr.* **1997**, submitted.

15) There are at least two mechanistic pathways leading to **9** which will be discussed in a full paper. Compound **10** is probably the result of a Lewis acid promoted rearrangement of **2c**.

16) For related observations in ketyl-olefin cyclizations leading to cyclopentane derivatives see: Molander, G. A.; McWilliams, J. C.; Noll, B. C. *J. Am. Chem. Soc.* **1997**, *119*, 1265.

17) For α-hydroxylation of enolates with oxygen see: Jones, A. B. in *Comprehensive Organic Syntheses* (Eds. Trost, B. M.; Fleming, I.) *Vol. 7*, p. 151, Pergamon Press, Oxford **1991**.