Pergamon

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Tetrahedron Letters 44 (2003) 45–48

TETRAHEDRON LETTERS

Synthesis and PET oxidative cyclization of silyl enol ethers: build-up of quasi-steroidal carbocycles

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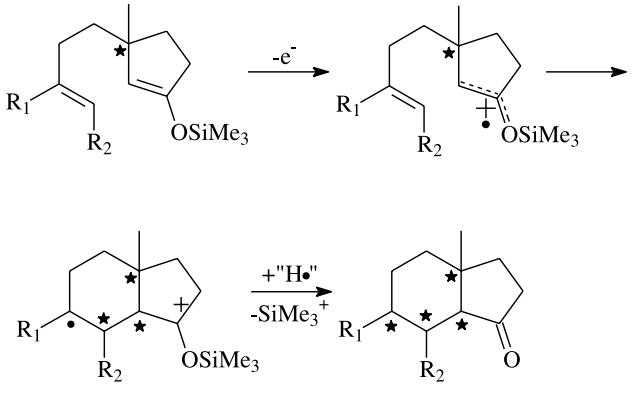
Received 30 October 2002; revised 6 November 2002; accepted 7 November 2002

Abstract—PET oxidative cyclization of silyl enol ethers carrying suitable side chains with olefinic double bonds results in the stereoselective formation of carbocycles. Two model compounds for investigating the influence of silyl enol ether ring size are synthesized. Furthermore the synthesis of a quasi-steroidal carbocycle with an unnatural configuration is presented. © 2002 Elsevier Science Ltd. All rights reserved.

The chemistry of electron deficient compounds is a major topic in recent research.[1] Silyl enol ethers represent a class of electron rich, non-aromatic compounds, which form reactive radical cations on one electron oxidation. There is a wide range of methods available to carry out one-electron oxidations on silyl enol ethers. Various metal ions like Ce(IV),[2] V(V),[3] other chemical oxidants like XeF_2,[4] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[5] anodic oxidation[6] and photoinduced electron transfer (PET)[7] can be used.



Scheme 1. Formation of silyl enol ether radical cation and ring closure reaction.

Besides processes like further oxidation,[5,7a,8] the intramolecular reaction with double bonds is the most important reaction of these electron deficient intermediates (Scheme 1).[2,6a,7d,e]

In our group, the PET oxidation of silyl enol ethers and subsequent ring closure reactions have been thoroughly investigated.[7d–f] In the course of this research, the regio- and stereoselective build-up of carbocycles turned out to be an aspect of synthetic importance. On basis of these findings, we planned a synthesis of steroid-like carbocycles by a cascade cyclization of silyl enol ethers.

The key structure of this synthetic strategy is a silyl enol ether moiety embedded in a carbocycle with a stereogenic center adjacent to the double bond (Scheme 1). This controls the stereochemistry of the stereogenic centers built up in the cyclization reaction.

Though silyl enol ethers derived from cyclic ketones have become an important class of precursors in organic chemistry, there are only a few general methods available for their selective synthesis.[9] One of the best-known ways for the regioselective build-up of the silyl enol ether double bond is the 1,4-addition of organocopper reagents to enones in the presence of trimethylsilyl chloride.[10] We employed this reaction for the addition of a methyl group to the desired enone. For the synthesis of the enone we used the lithiation of an iodide and addition of this organometallic intermediate to a cyclic vinylic ester.[11]

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PII: S0040-4039(02)02491-7

With this strategy on hand we have a flexible synthetic route towards variations of both ring size and side chain of the silyl enol ether.

The synthetic procedure was applied to the syntheses of silyl enol ethers **1** and **2** (Scheme 2) as model systems for investigating the influence of the silyl enol ether ring size on the stereochemistry of the cyclization.

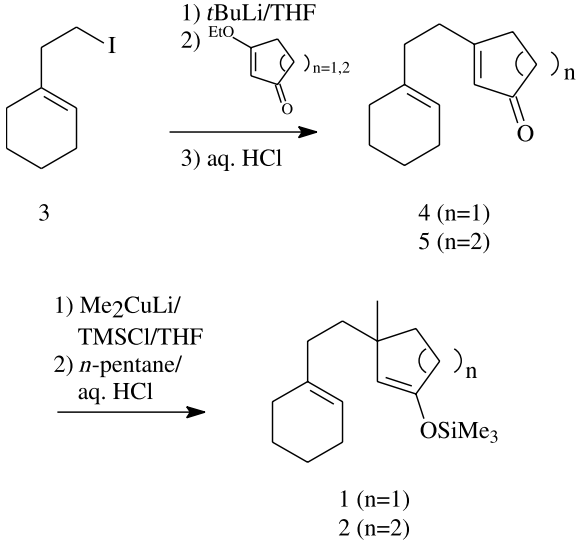
Iodide **3** was synthesized from cyclohexanone by known methods.[12] Enones **4** and **5** were synthesized by the described method in 60 and 61% isolated yields, respectively.

Silyl enol ethers **1** (74% yield) and **2** (85% yield) were obtained as racemic mixtures.

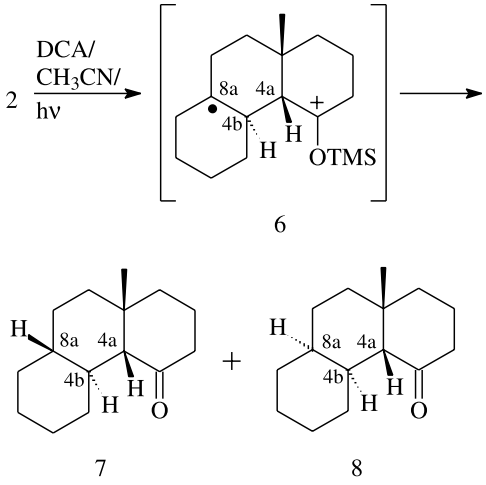
The PET oxidative cyclization of the six-membered ring silyl enol ether **2** with DCA (9,10-dicyano-anthracene) as sensitizer leads to the formation of two diastereomeric products **7** and **8** in a 90:10 ratio (49% combined isolated yield). Both cyclization products have the same 4a-4b-*transoid* ring connection (Scheme 3) resulting from a completely selective attack of the radical cation moiety of the initial radical cation on the cyclohexene double bond leading to the intermediate radical cation **6**. The remaining stereogenic center **8a** is generated by the saturation of the intermediate radical function in **6** from different sides of the molecule (Scheme 3). Here a second selectivity is observed yielding the 90:10 ratio of the products.

In contrast, the cyclization of **1** with DCA as sensitizer leads to the formation of the diastereomeric products **9**, **10** and **11** with a 41:31:28 ratio in 42% combined isolated yield (Scheme 4).

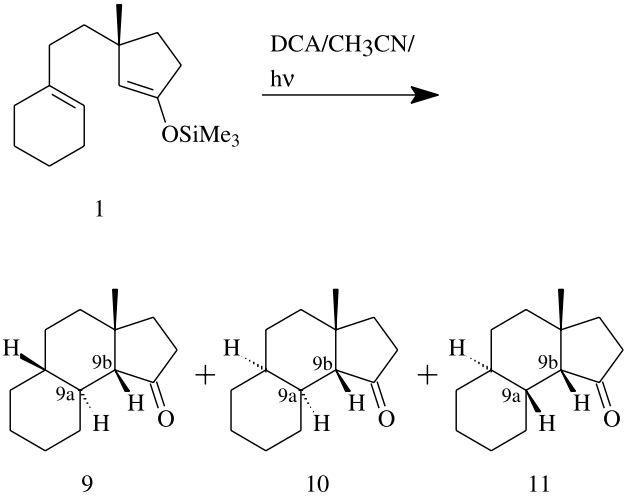
Obviously the change in ring size has a large effect on the selectivity of the cyclization reaction. Products **9** and **10** are formed in analogy to **7** and **8**. Product **11** is formed by an attack of the radical cation on the



Scheme 2. Syntheses of model silyl enol ethers **1** and **2**.



Scheme 3. PET oxidative cyclization of **2**.



Scheme 4. PET oxidative cyclization of **1**.

cyclohexene double bond with both rings almost stacked, leading to a 9b-9a-*cisoid* ring connection. This mode of ring closure does not occur in the reaction of **2** and only yields one isolable product from the saturation of intermediate radical function,[13] presumably due to greater differences in transition state energies in the two possible saturation pathways.

The structure determination of **1**–**5** and **7**–**11** has been accomplished with NMR spectroscopy (^{1}H, ^{13}C, DEPT, HSQC, HMBC), MS(EI), HRMS and IR. The assignment of configuration in the cyclization products **7**, **8**, **9**–**11** has been carried out with NMR spectroscopy by NOESY experiments in combination with determination of all necessary ^{1}H/^{1}H coupling constants and comparison of these results with the geometry of the possible diastereomeric cyclization products obtained by calculation of conformer distributions on semi-empirical level (AM1).

To explore the possibilities of syntheses of steroidal tetracycles by cascade cyclizations of silyl enol ether radical cations, we chose a silyl enol ether with a

six-membered ring and a side chain derived from (*S*)-perillyl alcohol **12** (Scheme 5). Iodide **13** was synthesized in 53% yield from **12** in analogy to known methods.[14] The described strategy leads to the formation of enone **14** (64% yield) and silyl enol ether **15** (84% yield) as an inseparable mixture of the two diastereomers.

PET oxidative cyclization in a solvent mixture of acetonitrile and propionitrile with DCA as sensitizer results in the formation of three products **16**,[15] **17**[16] and **18** in a 47:41:12 ratio. The combined isolated yield is 28%. The two major products **15** and **16** are formed from one of the two diastereomeric silyl enol ethers **14**. Compounds **16** and **17** are generated by the same modes of cyclization in the two ring closure steps and the same mode of saturation of the remaining radical function. The first ring closure can be seen in analogy to the cyclization of **2**, the second ring closure results from an attack of the tertiary radical center on the trisubstituted cyclohexene double bond. For this type of radical cyclization reaction other authors have also observed a *trans*,*anti*-stereochemistry.[17]

Compounds **16** and **17** have been isolated from a mixture of cyclization products by preparative HPLC and fractional crystallization. Byproduct **18** was obtained as an inseparable mixture with **17** only. ^{13}C NMR and DEPT were measured, revealing the same carbon backbone as in **16** and **17**. Presumably **18** is the result of a different mode of saturation of one of the diastereomeric intermediate radicals.

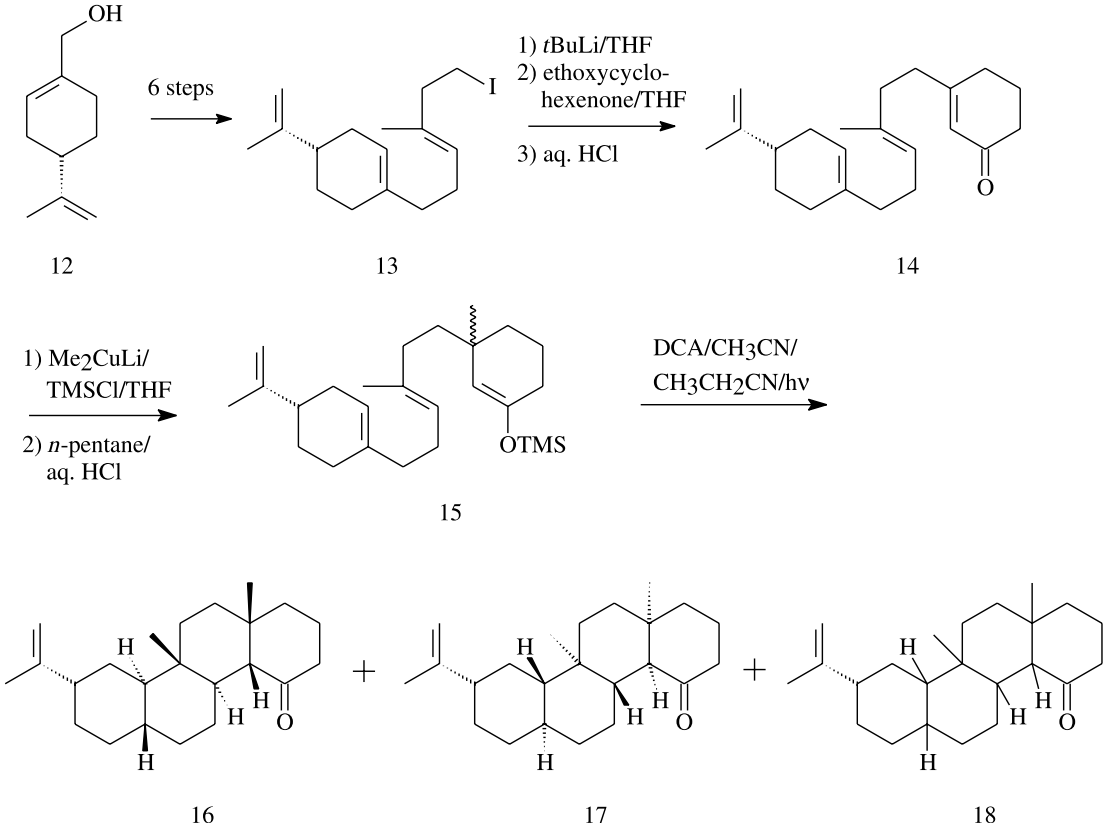
In conclusion, we presented a new synthetic strategy for building up polycyclic carbon frameworks by cascade cyclization utilizing silyl enol ethers as a source of reactive radical cations. The syntheses of two sets of model compounds for investigating the influence of silyl enol ether ring size revealed interesting stereochemical features. The underlying mechanism with regard to the stereoselectivity of the ring closure reaction and the saturation mechanism are subject to current research. Furthermore, by cascade cyclization a carbon backbone is accessible that represents an unnatural quasi-steroid concerning the attachment of the 19-methyl group[18] and the C/D-*cis* ring juncture. Both features are hard to synthesize by other means. This cascade cyclization shows a remarkable stereoselectivity, which makes it a useful way of preparing these molecules with stereochemical features not available by established methods.

Supplementary material

Analytical data for compounds **1**–**5**, **7**–**18**. Synthetic schemes and analytical data for the synthesis of **13** from **12** are available from the author.

Acknowledgements

Financial support by the Ministerium für Schule, Wissenschaft und Forschung des Landes Nordrhein-



Scheme 5. PET oxidative cascade cyclization of **1**.

Westfalen (MSWF-NRW), the Deutsche Forschungsgemeinschaft (DFG), the Fonds der Chemischen Industrie and the Innovationsfonds der Universität Bielefeld is gratefully acknowledged. We also thank the state of Nordrhein-Westfalen for granting a predoctoral scholarship for J.O.B.

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13. 'Isolable' should be understood in the way, that if the relative intensity of the two possible products **11** and corresponding isomer is roughly 95:5, due to the presence of **9** and **10** in the mixture of cyclization products the overall relative intensity is less than 2%; traces of products with correct MS spectra can be detected with GC/MS, but not isolated.
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15. Structure assigned by X-ray structure analysis. Crystallographic data (excluding structure factors) for this structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 196357.
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