ORGANIC LETTERS

2008
Vol. 10, No. 19
4195−4198

7-Silylcycloheptatrienes and Analogues: Reactivity and Selectivity in Cascade Processes

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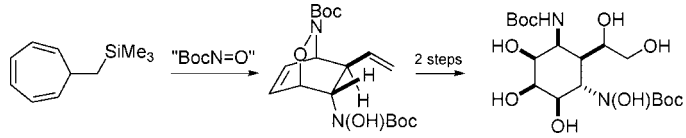
Received July 18, 2008

ABSTRACT



7-Silyl- and 7-silylmethylcycloheptatrienes react with acylnitroso reagents at room temperature to provide the corresponding silyl- and silymethylnorcaradiene cycloadducts. Depending on the reaction conditions, 7-silylmethylcycloheptatriene was also shown to provide, through cascade processes, functionalized cyclohexa-1,3-dienes or bicyclic synthons, incorporating one and two amino groups, respectively, that may be elaborated further, for instance, into sugar mimics.

Valence isomerism between cycloheptatriene **I** and norcaradiene **II** has attracted considerable interest for more than 40 years (Scheme 1).[1] Electron-withdrawing substituents (R = CO_2R, CHO, CN) at C7 tend to shift the equilibrium toward the norcaradiene form, whereas π-electron donating groups (OR, NR_2) tend to favor the cycloheptatriene, observations that were rationalized invoking internal charge-transfer complex[1c,d] and simple HOMO−LUMO interactions.[2] Other more sophisticated orbital pictures have been devised that predict the effects of substituents on these equilibria.[3] The presence of small equilibrium concentrations of the norcaradiene form was confirmed using Diels−Alder reactions.[1b,4]

Scheme 1. Cycloheptatriene−norcaradiene Equilibrium

Cyclohepatriene **I** Norcaradiene **II**

R = CO_2R', CN, CHO, OR, NR_2, SiR_3

Interestingly, while the above equilibrium has been studied on cycloheptatrienes having various electronically differentiated substituents,[1b] very little is known about the reactivity of silyl-substituted cycloheptatrienes (**I**, R = SiR_3) and their silylmethyl homologues (**I**, R = CH_2SiR_3).[5] The SiR_3 group is recognized as a σ-donating but also π-acceptor substituent,[6] and the intrinsic properties of silicon should affect the chemistry of the above polyenes as well as the position of the equilibrium during Diels−Alder reactions. In the course of our studies on silylated polyenes,[7] we recently started an

(1) (a) Maier, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 402–413. (b) Adam, W.; Balci, M.; Pietrzak, B. *J. Am. Chem. Soc.* **1979**, *101*, 6285–6291. (c) Ciganek, E. *J. Am. Chem. Soc.* **1965**, *87*, 652–653. (d) Ciganek, E. *J. Am. Chem. Soc.* **1967**, *89*, 1454–1458.

(2) (a) Hoffmann, R. *Tetrahedron Lett.* **1970**, *11*, 2907–2909. (b) Günter, H. *Tetrahedron Lett.* **1970**, *11*, 5173–5176.

(3) (a) Tang, T.-H.; Lew, C. S. Q.; Cui, Y.-P.; Capon, B.; Csizmadia, I. G. *J. Theochem. Struct.* **1994**, *305*, 149–164. (b) Mealli, C.; Ienco, A.; Hoyt, E. B., Jr.; Zoellner, R. W. *Chem. Eur. J.* **1997**, *3*, 958–968.

(4) (a) Wahl, G. H. *J. Org. Chem.* **1968**, *33*, 2158–2159. (b) Bordner, J.; Wahl, G. H. *J. Org. Chem.* **1971**, *36*, 3630–3631. (c) Jenner, G.; Papadopoulos, M. *J. Org. Chem.* **1986**, *51*, 585–589. (d) Masakatsu, M.; Tamaki, S.; Hiroshi, M.; Masaaki, A.; Satoshi, A. *J. Chem. Soc., Chem. Commun.* **1995**, 101–102. (e) Goldstein, M. J.; Gevirtz, A. H. *Tetrahedron Lett.* **1965**, *6*, 4413–4416.

(5) Ashe, A. J, III *J. Org. Chem.* **1972**, *37*, 2053–2054.

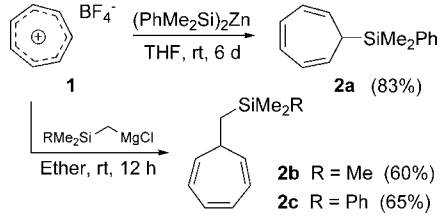
(6) Bassindale, A. R.; Taylor, P. G. In *The chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons, Ltd.: Chichester, 1989; Part 2, p 893.

10.1021/ol8016403 CCC: $40.75
Published on Web 09/10/2008

investigation on the synthesis and the reactivity of silylcycloheptatrienes such as **I** (Scheme 1, R = SiR_3, CH_2SiR_3). We report here that reactive dienophiles such as acylnitroso reagents interfere with **I**−**II** equilibrium in cycloadditions performed at ambient temperature, leading to the corresponding norcaradiene adducts in excellent yields. Interestingly, these cycloadducts are also valuable intermediates, and their subsequent transformations, depending on the nature of the silyl substituents and the reaction conditions, afford a straightforward access to highly funtionalized targets.

Three silylcycloheptatrienes were first prepared. The synthesis of silylcycloheptatriene **2a** using the CuCl-catalyzed silyldiazomethane addition to benzene,[8] requiring the tedious synthesis of the corresponding diazo compound, was not found suitable for gram scale synthesis. We thus devised an alternative and simpler approach, involving the silylation of tropylium salt **1**, using $(PhMe_2Si)_2Zn$[9,10] in THF (Scheme 2). This produced **2a** as a single isomer in excellent

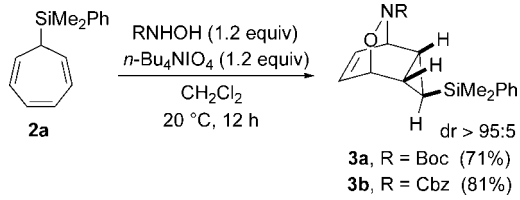
Scheme 2. Synthesis of Silylcycloheptatrienes **2a**−**c**



yield. This method is more general that the one previously reported and should be applicable to other arylsilyl analogues. Silylcycloheptatrienes **2b** and **2c** were prepared from **1**, following White's procedure,[11] and were also obtained in reasonable yields.

Silylcycloheptatriene **2a** was first reacted with an acylnitroso reagent generated in situ from BocNHOH[12] and led, through a hetero-Diels−Alder process (HDA), to the formation of the cycloadduct **3a** in excellent yield as a single isomer, the structure of which was determined through X-ray diffraction studies (Scheme 3). A similar result was obtained

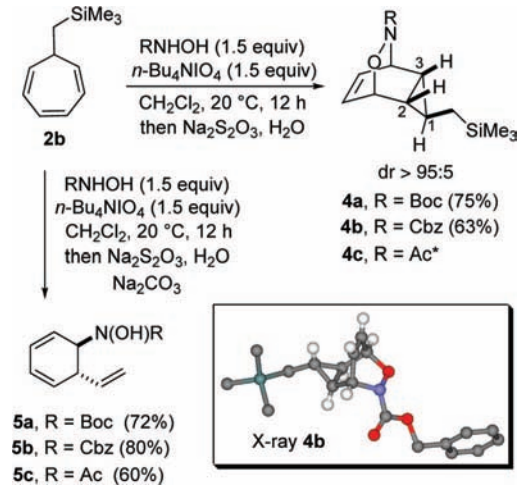
Scheme 3. Nitroso Cycloaddition onto Silylcycloheptatriene **2a**



with the *N*-Cbz-protected nitroso species (e.g., **3b**). These experiments establish without ambiguity the stereochemistry of silyl norcaradiene cycloadducts and show that a certain amount of the transient norcaradiene species **II** (R = $SiMe_3$) is present in solution, under the above cycloaddition conditions. It also indicates that the silylnorcaradiene valence isomer displays a dienic reactivity toward acylnitroso reagents greater than that of the silylcycloheptatriene at room temperature.[13]

Under similar conditions, silylmethylcycloheptatriene **2b** led to cyclopropanes **4a**−**c** having the same relative configuration as **3a,b** (e.g., X-ray of **4b**, Scheme 4). Remarkably,

Scheme 4. Nitroso Cycloaddition onto Silylcycloheptatriene **2b**



*Unstable, pure enough (^{1}H NMR) to be used without purification.

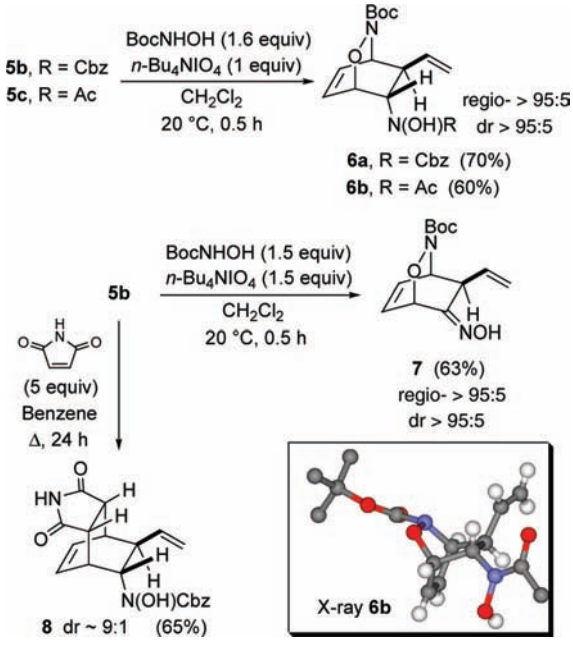
the workup of the cycloaddition process on precursor **2b** was found to be critical. For instance, treatment of the reaction mixture with aqueous $Na_2S_2O_3$, to remove the excess of periodate, led exclusively to **4a**−**c**. In sharp contrast, the use of aqueous $Na_2S_2O_3/Na_2CO_3$ led instead to the formation of vinyl-1,4-dienes **5a**−**c** as the only detectable regioisomers in good yields (Scheme 4). The formation of the vinyl group probably occurs through the ring opening of the cyclopropane moiety of **4a**−**c**, with concomitant desilylation. Silylmethylcyclopropanes are known to open under electrophilic and nucleophilic conditions, generating the corresponding unsaturated system.[14] Interestingly, treatment of pure cycloadduct **4b** under basic (Na_2CO_3/H_2O) or neutral ($NaBF_4$ in

(7) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369–1395.
(8) Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080–1082.
(9) (a) Morizawa, Y.; Oda, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1163–1166. (b) Oestreich, M.; Weiner, B. *Synlett* **2004**, 2139–2142.
(10) $PhMe_2SiLi$ in THF did not react with **1**.
(11) Hassall, K. S.; White, J. M. *Org. Lett.* **2004**, *6*, 1737–1739.
(12) (a) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (b) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107–1117. (c) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873–879. (d) Bodnar, B. S.; Miller, M. J. *J. Org. Chem.* **2007**, *72*, 3929–3932. (e) Krchnak, V.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Comb. Chem.* **2008**, *10*, 94–103.
(13) For cycloadditions involving the cycloheptatriene form, see: (a) Adam, W.; Balci, M. *J. Am. Chem. Soc.* **1979**, *101*, 7542–7547. (b) Pearson, W. A.; Mans, D. M.; Kampf, J. W. *J. Org. Chem.* **2004**, *69*, 1235–1247. (c) Templin, S. S.; Wallock, N. J.; Bennett, D. W.; Siddiquee, T.; Haworth, D. T.; Donaldson, W. A. *J. Heterocycl. Chem.* **2007**, *44*, 719–723.

CH_3CN-H_2O) conditions also led to dienes **5b** as sole products, indicating that ionization of the allylic C−O bond likely promotes the cyclopropane ring opening (see discussion below). The complete regioselectivity during the cyclopropane ring opening in **4a**−**c** is also striking and may be attributed to the higher electronegativity of oxygen relative to that of nitrogen, resulting in a weakening of the strength of the cyclopropane C1−C2 bond, antiperiplanar to the C−O bond. Examination of the X-ray structure of **4b** effectively showed that the cyclopropane C1−C2 bond is slightly longer (1.511 Å) than the C1−C3 bond (1.506 Å).

Although dienes **5a**−**c** proved to be relatively fragile, cycloadition reaction with a second nitroso reagent was carried out leading to cycloadducts **6a,b** in good yields (Scheme 5). Varying the nature of the nitroso reagents in

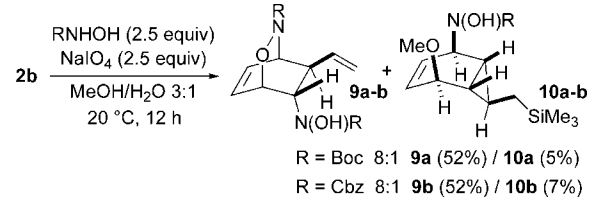
Scheme 5. Nitroso Cycloaddition onto Cyclohexadienes **5b,c**



both cycloadditions thus allowed the introduction of orthogonally protected amino groups and generation of four contiguous stereocenters in only two steps from **2b**. It is worth noting that *complete regio- and diastereocontrol were observed*, with the nitroso reagent approaching *anti* relative to the hydroxyaminyl moiety and the incoming *N*-Boc substituent on the side of the vinyl group (e.g., X-ray structure of **6b**). Yields of **6a,b** also depend on the amount of oxidizing agent used for the generation of the nitroso reagent. Overoxidation was observed when 1.5 equiv of periodate was used, affording oxime **7**,[15] which indicates that Cbz is a good leaving group under those conditions. Finally, other dienophiles such as maleimide react with **5b** to give, with good diastereocontrol, the *endo*-cycloadduct **8** in reasonable yield.[16]

The stability of cycloadducts **4a**−**c** was also questioned when the nitroso cycloaddition was performed using $NaIO_4$ in $MeOH/H_2O$ (Scheme 6). Under these conditions and an

Scheme 6. Nitroso Cycloaddition onto Silylcycloheptatriene **2b** in $MeOH-H_2O$



excess of hydroxylamine, **2b** led to cycloadducts **9a,b**, along with separable minor products **10a,b**, obtained as single diastereomers.[17] When the reaction was carried out using BocNHOH (2 equiv) in pure MeOH, a 3:1:4 mixture of **9a**/**10a**/**5a** was formed, further indicating the major influence of the polarity of the solvents on the product outcome.

A general mechanism, taking into account the polarity of the medium and rationalizing the formation of cycloadducts **4**, dienes **5**, bicyclic products **9**, and byproduct **10**, may thus be proposed (Figure 1). The experiments above argue in favor

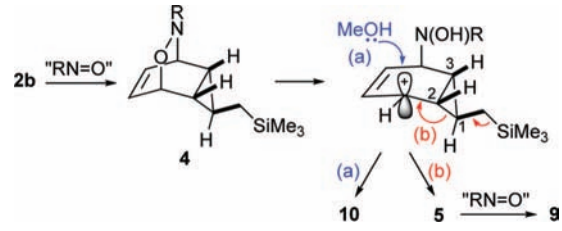


Figure 1. Postulated mechanism of the cascade.

of silylnorcaradienes **4** as key intermediates in the process. These are generated from cycloheptatriene **2b** as unique products and are stable in weakly polar medium (CH_2Cl_2) (Scheme 4). In constrast, in polar media ($MeOH-H_2O$) and even under neutral conditions ($NaBF_4$ in CH_3CN-H_2O), **4** rearranges into **5**. This probably occurs through the ionization of the allylic C−O bond of **4** and results in the formation of a putative carbocation intermediate.[18,19] The latter may then

(14) (a) Ryu, I.; Hirai, A.; Suzuki, H.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1990**, *55*, 1409–1410. (b) Fleming, I.; Sanderson, P. E. J.; Terrett, N. K. *Synthesis* **1992**, 69–74. (c) Panek, J. S.; Garbaccio, R. M.; Jain, N. F. *Tetrahedron Lett.* **1994**, *35*, 6453–6456. (d) Mohr, P. *Tetrahedron Lett.* **1995**, *36*, 7221–7224. (e) Kihihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 6907–6910. (f) Angelaud, R.; Landais, Y. *Tetrahedron Lett.* **1997**, *38*, 8841–8844. (g) Angelaud, R.; Landais, Y.; Parra-Rapado, L. *Tetrahedron Lett.* **1997**, *38*, 8845–8848. (h) Landais, Y.; Parra-Rapado, L. *Eur. J. Org. Chem.* **2000**, *2*, 401–418.

(15) Reduction of **7**, using $NaBH_3CN$ in AcOH led to the desired hydroxylamine having the same stereochemistry than **6a,b**.

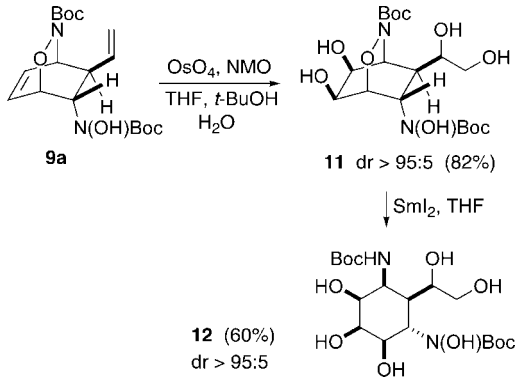
(16) The relative stereochemistry was assigned based on NOESY connectivities (see Supporting Information).

(17) NOESY connectivities were used to establish unambigously the relative configuration of **10a** (see Supporting Information). By analogy, the same configuration was assigned to **10b**.

be trapped by the solvent (MeOH) to afford cyclohexenes **10** as minor compounds (route a).[20] A competing pathway, involving a cationic-mediated cyclopropane ring opening (route b), would in turn lead to dienes **5**. This route is favored by the presence of the electron-releasing silicon group and the proper alignment between the σ_{C-Si} bond and the C1−C2−C$^+$ moiety. Similar C−O bond cleavage was observed with cycloadducts **3** (Scheme 3), leading exclusively to nucleophilic attack by MeOH or H_2O. In this case, the cyclopropane ring opening is probably much slower as the carbocation at C1, issued from the C1−C2 bond cleavage, is α to silicon and not β as in **4**.[21] Finally, the formation of **9** results from an unprecedented hetereo domino process,[22] involving a pericyclic (HDA)−cationic (cyclopropane ring opening)−pericyclic (HDA) process, the second cycloaddition occurring on dienes **5**.

The synthesis of cycloadducts **9a,b** in a single pot operation from cycloheptatriene **2b** with complete regio- and sterecontrol also provides a unique entry toward highly functionalized amino-carbasugars and analogues, as illustrated with the elaboration of amino-polyol **12** (Scheme 7). Dihydroxylation of **9a** under Upjohn conditions afforded

Scheme 7. Rapid Access to the Amino-Carbasugar Skeleton



11 as a single diastereomer with the stereochemistry as shown.[23] The N−O bond was then cleaved under reductive conditions to provide cyclohexane **12**, as a unique detectable isomer, having seven contiguous stereogenic centers installed in only four steps from tropylium **1**.

As a summary, we reported the synthesis and a straightforward functionalization of 7-silyl- and 7-silylmethylcycloheptatrienes through an unprecedented nitroso hetero-Diels−Alder (HDA)−silicon-directed cyclopropane ring opening cascade. This process gives rise to functionalized dienes that may be elaborated further, for instance, toward sugar mimics. Further manipulations of these simple intermediates and development of an enantioselective version of this cascade is currently underway in our laboratories.

Acknowledgment. We thank the CEFIPRA program for a grant to R.B. and financial support. We are grateful to Dr. B. Kauffmann (IECB, Bordeaux) for X-ray diffractions studies and J. C. Lartigue and N. Pinaud (ISM, University Bordeaux-1) for NMR experiments. We also thank Ms. N. Kounchieu (ISM, University Bordeaux-1) for the synthesis of **2a** and Dr. F. Robert (ISM, University Bordeaux-1) and Prof. G. Mehta (Indian Institute of Science, Bangalore, India) for helpful discussions.

Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Treatment of **4a** with *n*-Bu_4NF led to recovered starting material, indicating that the cyclopropane ring opening was not initiated through nucleophilic attack at silicon.[14g]

(19) For a recent observation of acid-sensitive acylnitroso Diels−Alder cycloadducts reported, while this work was under progess, see: Krchnak, V.; Moellmann, U.; Dahse, H.-M.; Miller, M. J. *J. Comb. Chem.* **2008**, *10*, 112–117.

(20) A directing effect of the resident allylic carbamate probably operates, through hydrogen bonding with MeOH, explaining the approach of the nucleophile on the *syn* face.

(21) The β-silicon effect may be invoked to rationalize this cationic silylmethylcyclopropane ring opening.[14] Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677–2689, and references therein.

(22) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

(23) NOESY connectivities were used to determine the relative configuration of **11** and hence establish the *exo* approach of the osmium reagent. The stereochemistry of the exocyclic OH group could not be determined using NMR experiments.