Tetrahedron 72 (2016) 6025–6030

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper and silicon mediated, HMPA-free, n+3 ring expansions for the construction of medium sized lactones and lactams: short synthesis of (+)-*cis*-lauthisan

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ARTICLE INFO

Article history:
Received 22 April 2016
Received in revised form 11 May 2016
Accepted 23 May 2016
Available online 28 May 2016

Keywords:
Medium sized lactones
Ketone enolates
Epoxide ring opening
Ring expansion
Total synthesis

ABSTRACT

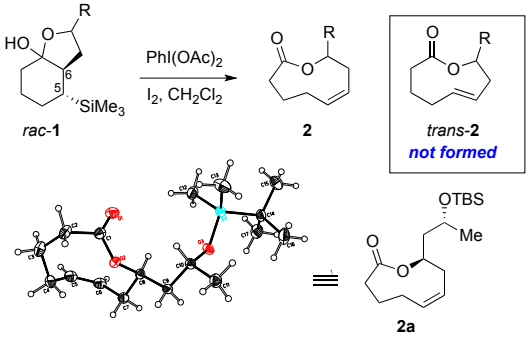
In this report, several new epoxide examples were united with β-silyl ketone enolates for the construction, after oxidative fragmentation, of ring expanded lactones, n+3 atoms in size. Importantly, azido lactones were found to be valuable in an extension of this protocol involving the n+3+p expansion into a series of hydroxyolefinic lactams. We also document a short, stereoselective total synthesis of (+)-*cis*-lauthisan and a new, cuprate-mediated and HMPA-free procedure for the generation of β-silyl silylenol ethers, useful in the environmentally-friendly construction of medium sized lactones.

1. Introduction

Pursuing our interest in epoxide ring opening reactions for the construction of medium sized lactones[1] and lactams,[2] we initiated a detailed investigation into our three-step, silicon-mediated n+3 ring expansion process with respect to substrate scope and overall efficiency. For example, the major advantage of this method over our previously reported two-step procedure[3] was the replacement of toxic tin and lead reagents [$LiSnBu_3$ and $Pb(OAc)_4$, respectively] with environmentally-friendly sources of silicon (Me_3SiLi) and hypervalent iodine [$PhI(OAc)_2$, I_2]. Unfortunately, however, in order to generate the requisite β-silyl enolate, it was necessary to employ hexamethylphosphoramide (HMPA); a polar aprotic solvent which is known to be highly toxic. Also of note, a comprehensive substrate scope, in terms of reactive functionality on the epoxide sidechain, was not undertaken in either of our initial reports. Herein, we address both of these deficiencies and also provide a showcase for this method with the synthesis of ring expanded lactams and the stereoselective construction of (+)-*cis*-lauthisan.

2. Mechanistic investigations

As mentioned above, the success of our n+3 ring expansion method relies upon the use of hypervalent iodine to fragment β-silyl hemiketal intermediates (cf. **1**, Scheme 1), formed via the union



Scheme 1. Hemiketal oxidative fragmentation and lactone ORTEP.

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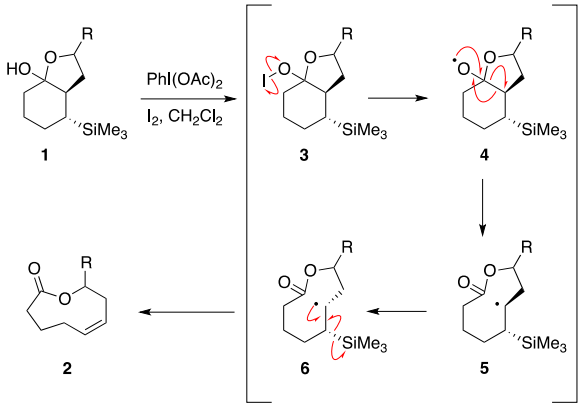
http://dx.doi.org/10.1016/j.tet.2016.05.063
0040-4020/

of β-silyl ketone enolates with epoxides, into lactones (cf. **2**) with exclusively C(5)–C(6) *cis*-alkene geometry (*n*=5 and 6). Said differently, when utilizing either cyclopent- or cyclohex-enone as starting material, despite the *trans*-orientation between the hydrogens of their corresponding β-silyl hemiketals, we have not observed any *trans*-alkene containing lactone products.

The observed stereochemical preference for this reaction was initially somewhat of a mystery, especially when one considers the anionic fragmentation mechanism that was operative in our earlier work[3] and led to *trans*-alkenes as major products. Importantly, the *cis*-geometry was unambiguously confirmed in two ways: (1) via calculation of the alkene proton coupling constant ($J=\sim 10$ Hz) of the resultant acyclic diols obtained after DIBAl-H reduction, and (2) the X-ray crystal structure of lactone **2a** which is representative of the nine-membered ring series (Scheme 1). On a related note, to the best of our knowledge, there have been no other literature reports that exploit the Suárez reaction conditions [$PhI(OAc)_2$, I_2][4] for the oxidative fragmentation of a β-silyl hemiketal such as **1**.

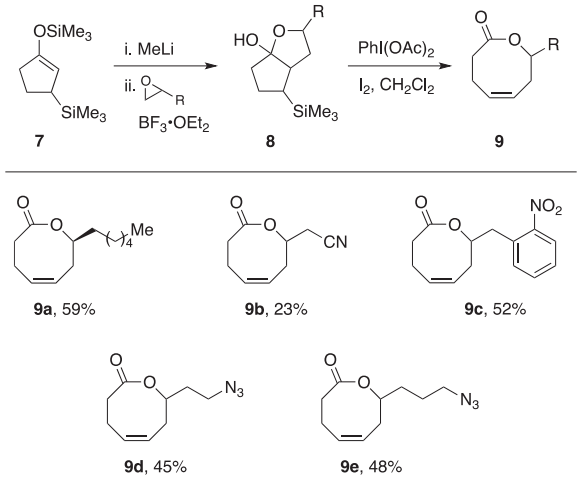
After considering these data, as well as several literature reports concerning similar fragmentation reactions,[5] we now propose the following, nonconcerted, fragmentation mechanism to account for *cis*-alkene formation (Scheme 2). In the absence of photochemical irradiation, hypoiodite **3**, formed upon the sequential addition of $PhI(OAc)_2$ and I_2 to a solution of **1** in CH_2Cl_2 at 0 °C, homolytically cleaves to form oxygen-centered radical **4** which subsequently undergoes bond scission to generate a lactone carbonyl and β-silyl carbon centered radical **5**. Previously, Kochi and co-workers observed that β-silyl radicals of this nature can be stabilized through hyperconjugation between the half filled radical p-orbital and the filled carbon–silicon σ-orbital.[6] For this to occur in our system, carbon–carbon bond rotation must occur, resulting in an eclipsed conformation (**6**) before final fragmentation and olefin formation, orienting the C(5)–C(6) hydrogens *cis* to one another in the product (Scheme 2).



Scheme 2. Proposed hemiketal oxidative fragmentation mechanism.

3. Construction of novel eight-membered lactones

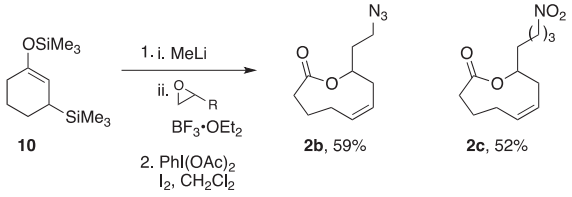
In addition to cyclohexenone, we have also reported that the β-silyl silylenol ether of cyclopentenone (**7**) can be exploited for the synthesis of eight-membered (5+3) lactones (cf. **9**, Scheme 3).[1] However, while reexamining our initial work, the substrate scope seemed somewhat limited, with silyl and benzyl protected alcohols the only reported functional groups tolerant of the two-step procedure. We now wish to report several additional reactive moieties that can survive both the epoxide opening step and subsequent oxidative fragmentation conditions (Scheme 3).



Scheme 3. 5+3 Ring expansion for the construction of eight-membered rings.

Several epoxide examples[7] in Scheme 3 are noteworthy. In addition to chiral, non racemic epoxides (cf. **9a**),[8] masked amine functionality, notably terminal nitriles (**9b**), aromatic nitro groups (**9c**), and azides (**9d–e**) are exceedingly competent. Two step yields for these lactones are generally good with the notable exception being allyl cyanide oxide, where the poor yield may be attributed to epoxide volatility and/or α-proton acidity.

Related to this study, we also united two new epoxide examples with the enolate corresponding to six-membered enol ether **10** (Scheme 4).[1] Not surprisingly, 4-azidobutene oxide produced the desired lactone in comparable yield to **7** (cf. **2b** vs **9d**), while a terminal aliphatic nitro group with acidic α-protons was also surprisingly able to withstand the reaction conditions.



Scheme 4. 6+3 Ring expansion for the construction of nine-membered rings.

4. Lactone to lactam ring expansions

In 2005, we published a short report regarding the sequential ring expansions of n-sized cycloalkenones into hydroxyolefinic n+3+p sized lactones,[1b] where translactonization was efficiently triggered by fluoride mediated silyl ether cleavage. After the success of this work, we sought to develop an analogous protocol for the conversion of lactones into ring expanded lactams, especially in light of our related studies on the synthesis of δ-lactams via lactone ring contraction.[2] In a similar way, we had hoped that azido lactones **9d–e** and **2b** would serve as suitable substrates for this purpose.[9]

Initially, relying on the Corey method for azide reduction,[10] lactone **2b** was treated with hydrogen over the Lindlar catalyst (Scheme 5). While the desired chemoselective reduction did occur, concomitant intramolecular reorganization was not observed; primary amine **11** was isolated as the major organic product (80%). This result is surprising, especially when one considers the transition state required for lactam formation is six atoms in size. A variety of subsequent reaction conditions were screened, for example: heat, microwave irradiation, base treatment (Et_3N and K_2CO_3), and the addition of Lewis acids (e.g., $TiCl_4$, $CeCl_3$, Me_3Al, and