Pergamon

Tetrahedron Letters 44 (2003) 5407–5409

TETRAHEDRON LETTERS

# New silicon-mediated ring expansion of n-sized conjugated cycloalkenones into homoallylic n+3 lactones

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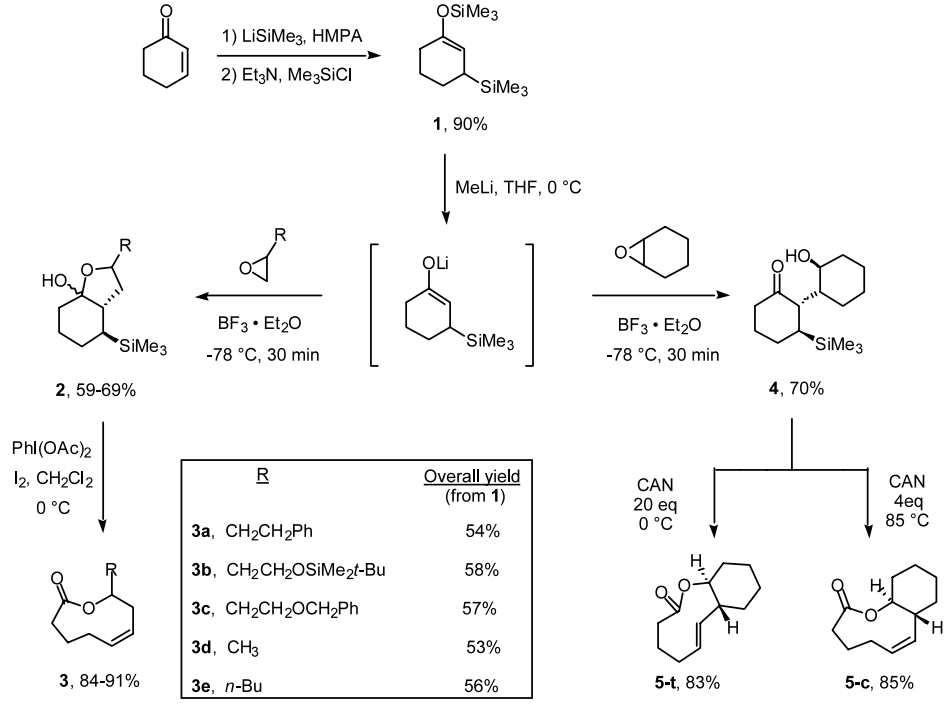
Received 11 April 2003; revised 23 May 2003; accepted 26 May 2003

**Abstract**—Silicon nucleophilic β-addition to various 2-cycloalkenones, followed ultimately by mild and rapid α-alkylation of the corresponding cycloalkanone enolates using diverse epoxides and $BF_3{\cdot}OEt_2$, produces useful γ-lactols and γ-hydroxyketones. Hypervalent iodine-promoted oxidative fragmentation then yields regiospecifically unsaturated, 3-atom ring expanded, 8–10 membered homoallylic lactones with good control of alkene geometry. © 2003 Elsevier Science Ltd. All rights reserved.

Pursuing our interest[1,2] in opening of epoxides by ketone enolate anions,[3,4] we report here new methodology for such reactions involving β-silylenolates. HMPA-promoted Michael addition of trimethysilyllithium[5] to 2-cyclohexenone and in situ enolate O-silylation produces bis-silylated product **1** (Scheme 1) that is stable at −20°C for several weeks and, therefore, that can be used as a stock solution. Enol silyl ether cleavage with methyllithium produces the corresponding β-silylenolate that rapidly opens monosubstituted epoxides at −78°C in the presence of $BF_3{\cdot}OEt_2$ (Scheme 1).




| R | Overall yield (from **1**) |
|---|---|
| **3a**, $CH_2CH_2Ph$ | 54% |
| **3b**, $CH_2CH_2OSiMe_2t$-Bu | 58% |
| **3c**, $CH_2CH_2OCH_2Ph$ | 57% |
| **3d**, $CH_3$ | 53% |
| **3e**, *n*-Bu | 56% |

**Scheme 1.**

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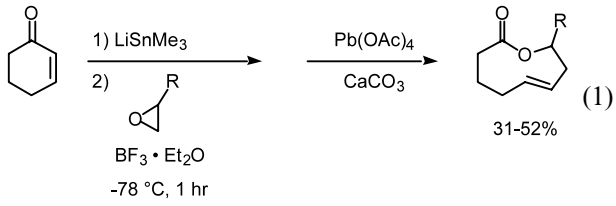
doi:10.1016/S0040-4039(03)01308-X

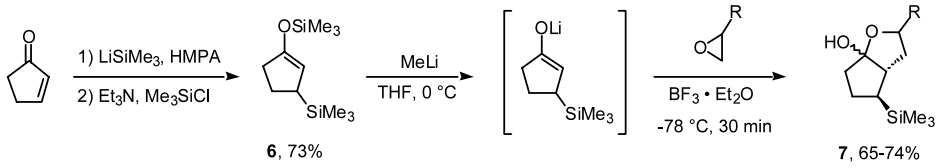
Several aspects of Scheme 1 are noteworthy. Direct epoxide opening by the initial β-silylcyclohexanone enolate formed in the first step of Scheme 1 in the presence of HMPA was not successful, due presumably to the undesirable Lewis base–Lewis acid interaction between HMPA and $BF_3{\cdot}OEt_2$. Oxidative fragmentation[6,7] of γ-hydroxysilanes **2** with hypervalent[8a] iodobenzene diacetate and molecular iodine[8b] proceeded stereoselectively in the absence of photochemical irradiation, presumably via a hemiketal hypoiodite intermediate,[8c] to provide *cis*-lactones **3** in high yields. The *cis*-geometry of lactone **3a**, for example, was confirmed by *i*-$Bu_2AlH$ reduction into the corresponding acyclic vicinally disubstituted alkene showing a typical $^1H$ NMR *cis*-double bond H–H coupling constant of 10.8 Hz.[9] The overall yields of 48–52% from 2-cyclohexenone to 9-membered *cis*-homoallylic lactones **3** compare favorably with our previous results (31–52%) using environmentally less desirable tin and lead chemistry[1] that generates also stereoselectively 9-membered, but isomeric, *trans*-homoallylic lactones (Eq. (1)). In a control reaction, iodobenzene diacetate and iodine did not cause isomerization of such 9-membered *trans*-homoallylic lactones into the thermodynamically more stable *cis*-isomers.

β-Silylcyclohexanone enolate opening of cyclohexene oxide, a 1,2-disubstituted epoxide, produces γ-hydroxyketone **4** (rather than the corresponding cyclized hemiketal) (Scheme 1), as indicated by both $^1H$ NMR and IR spectroscopy.[2] Although iodobenzene diacetate and iodine failed to achieve oxidative fragmentation of β-ketosilane **4**, ceric ammonium nitrate (CAN)[10] succeeds; at 0°C, a large excess of CAN produces *trans*-homoallylic lactone **5-t** in 83% yield, whereas at 85°C, four equivalents of CAN produces *cis*-homoallylic lactone **5-c** in 85% yield. Apparently, the CAN-promoted formation of an intermediate β-silyl radical[11,12] that then forms an alkene double bond is subject to kinetic or thermodynamic control, with formation of lactones **5-t** or **5-c**, respectively.



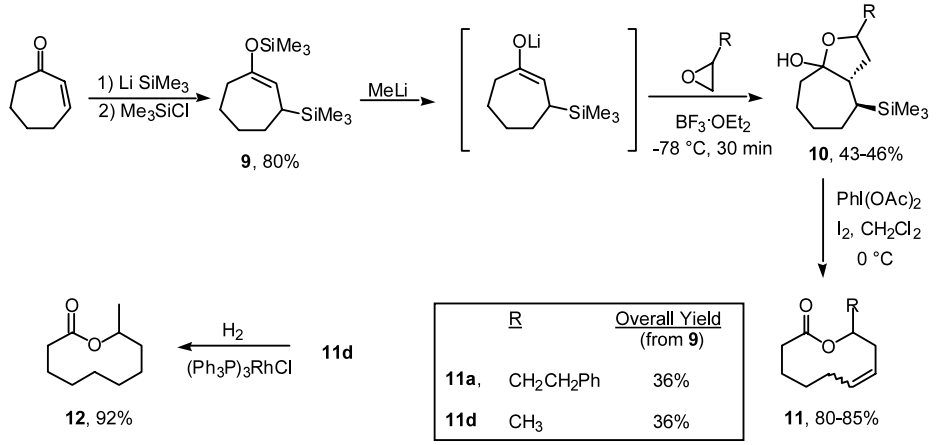
(1)

Both 5- and 7-membered conjugated cycloalkenones also undergo this silicon-mediated 3-atom ring expansion process (Schemes 2 and 3). Cyclopentenone-




| R | Overall yield (from **6**) |
|---|---|
| **8a**, $CH_2CH_2Ph$ | 58% |
| **8b**, $CH_2CH_2OSiMe_2t$-Bu | 52% |
| **8e**, *n*-Bu | 66% |

**Scheme 2.**




| R | Overall Yield (from **9**) |
|---|---|
| **11a**, $CH_2CH_2Ph$ | 36% |
| **11d** $CH_3$ | 36% |

**Scheme 3.**

derived β-silyl enol silyl ether **6** is stable at −20°C for several days. Hemiketals **7** are rapidly formed via $BF_3{\cdot}OEt_2$ promoted opening of several monosubstituted epoxides at −78°C. Iodobenzene diacetate and iodine stereoselectively convert γ-lactols **7** into 8-membered *cis*-homoallylic lactones **8** in 52–66% overall yields (Scheme 2). Cycloheptenone-derived β-silyl enol ether **9**, like **6**, is stable at −20°C for several days. γ-Lactols **10** are easily formed via $BF_3{\cdot}OEt_2$ promoted epoxide opening. Iodobenzene diacetate and iodine transform γ-lactols **10** into 10-membered homoallylic lactones **11** as a 1:1 mixture of double bond geometric isomers (Scheme 3). Reduction of the double bond in 10-membered homoallylic lactols **11d** produces fragrant natural product (±)-phoracantholide (**12**) in four steps and in 30% overall yield from 2-cycloheptenone.[1,13]

In summary, using silicon and hypervalent iodine rather than toxic tin and lead reagents allows 3-step 3-atom ring expansion of 5–7 membered cycloalkenones into more complex and thus more valuable 8–10 membered homoallylic lactones on gram scale and in overall 36–66% yields from stock solutions of bis-silylated intermediates **1**, **6**, and **9**.[14] An unusual but reliable and useful temperature effect was observed in the CAN-promoted oxidative fragmentation of β-silylketones **4**; low temperature kinetic control generates *trans*-homoallylic lactone **5-t**, whereas high temperature thermodynamic control produces the more stable *cis*-homoallylic lactone **5-c**. Study of the mechanism, the scope and limitations, and some complex natural product applications of these overall homologous Baeyer–Villiger[7] reactions will be reported in a full article.

## Acknowledgements

We thank Johns Hopkins University and the NSF for seed support of this project.

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14. A typical gram-scale experimental protocol follows:
**Hemi-ketal 2a**. To a 10 mL flask was added silylenol-ether **1**[5] (1.05 g, 4.33 mmol) and THF (6 mL). The solution was cooled to 0°C and MeLi (2.78 mL, 4.43 mmol, 1.60M in $Et_2O$) was added dropwise. After 10 min, the solution was cooled to −78°C and 4-phenyl-butene oxide (0.320 g, 0.320 μL 2.16 mmol) was added via syringe. The reaction was stirred for another 5 min at −78°C and $BF_3{\cdot}Et_2O$ (0.275 mL, 2.16 mmol, neat) was added very slowly (1 drop/5 s), while cooling the needle with a piece of dry ice. The reaction was quenched after 25 min with phosphate buffer (2 mL, pH 7.0) and warmed to rt. The mixture was extracted with $Et_2O$ (3×30 mL). The ether fractions were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining oil was purified by silica gel chromatography (85% hexanes, 15% ethyl acetate, $Et_3N$ ~3%) to give desired hemi-ketal **2a** (0.415 g) as a white solid (60% yield). Mp 91–92°C; $^1$H NMR ($CDCl_3$) $\delta$ 7.30–7.26 (m, 2H), 7.21–7.18 (m, 3H), 4.24–4.17 (m, 1H), 2.77–2.61 (m, 1H), 2.14–1.97 (m, 4H), 1.88–1.75 (m, 2H), 1.68–1.54 (m, 5H), 1.43–1.34 (m, 1H), 1.09–1.99 (m, 1H), 0.59–0.51 (m, 1H), 0.01 (s, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 142.04, 128.36, 128.30, 125.72, 105.26, 78.24, 44.82, 40.02, 37.25, 36.04, 32.57, 26.72 26.11, 24.33, −1.91; HRMS (CI) $m/z$ (M+Na) calcd. 341.1907 for $C_{19}H_{30}O_2SiNa^+$, found 341.1894.
**Lactone 3a**. Hemi-ketal **2a** (0.415 g, 1.303 mmol) was placed in a 25 mL flask with $CH_2Cl_2$ (8 mL, anhydrous) and cooled to 0°C. To this was added $PhI(OAc)_2$ (0.462 g, 1.433 mmol) and then $I_2$ (0.330 mg, 1.303, crystals). The reaction, which immediately turned a dark purple color, was stirred until starting material was consumned (TLC, ~4 h). The reaction was quenched with a saturated solution of sodium thiosulfate (5 mL) and stirred until colorless (~30 min). The mixture was diluted with $Et_2O$ (25 mL) and the organics were washed with $H_2O$ (2×, 25 mL) and dried over $MgSO_4$. The ether was removed under reduced pressure (no heat) and the remaining oil was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate) to give lactone **3a** (0.284 g) as a colorless oil (89% yield). $^1$H NMR ($CDCl_3$) $\delta$ 7.31–7.26 (m, 2H), 7.21–7.17 (m, 3H), 5.52–5.44 (m, 2H), 4.85–4.79 (m, 1H), 2.78–2.61 (m, 2H), 2.50 (m, 1H), 2.43–2.25 (m, 3H), 2.11–1.93 (m, 4H), 1.89–1.75 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 174.58, 141.59, 134.51, 128.40, 128.38, 125.89, 124.72, 72.92, 36.45, 34.14, 33.65, 32.13, 26.54, 25.29. IR ($Et_2O$, $cm^{-1}$) 3010, 2948, 2859, 1740, 1603, 1496, 1134; HRMS (CI) $m/z$ (M+Na) calcd. 267.135548 for $C_{16}H_{20}O_2Na^+$, found 267.134601.