ORGANIC LETTERS

2005
Vol. 7, No. 19
4301−4303

New Silicon-Mediated, Sequential Ring Expansions of *n*-Sized 2-Cycloalkenones into Hydroxyolefinic *n* + *m* + *p* Medium-Sized Lactones: Short Synthesis of (−)-Phoracantholide-J

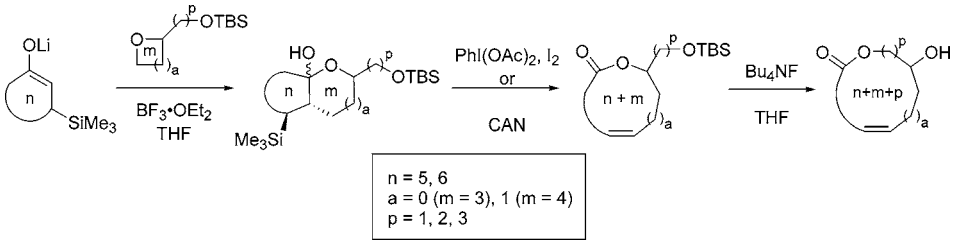
Gary H. Posner,* Mark A. Hatcher, and William A. Maio

Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218

ghp@jhu.edu

Received August 2, 2005

ABSTRACT



In only four steps from 2-cyclopentenone and 2-cyclohexenone, sequential three- or four-atom and then one- to three-atom ring enlargements produce nine- to 12-membered hydroxyolefinic lactones on a gram scale. 2-Cyclopentenone undergoes this serial 5 + 3 + 2 process to form 10-membered ring natural (−)-phoracantholide-J in six linear steps and 26% overall yield.

Organic chemistry is still being enriched by new synthetic methods for converting simple reactants into more complex compounds.[1] Specifically, transforming readily available carbocycles into much less common medium-sized rings remains an important goal, in part as an intellectual challenge and in part because many valuable natural products possess medium-sized rings.[2] Although many ring-expansion processes work well,[3] we have recently described a new three-step protocol using simple epoxides for overall homologous Baeyer−Villiger ring expansion of five- to seven-membered 2-cycloalkenones into eight- to 10-membered homoallylic lactones.[4] Now we report the first examples of oxetanes being opened by ketone enolate nucleophiles as well as significant enhancement of our carbocycle-to-heterocycle methodology using functionalized epoxides allowing preparation of more diverse, complex, and valuable medium-sized lactones.[5] Specifically, *β*-silyl *n*-sized cyclic ketone enolates open O-protected hydroxy-epoxides[6] or hydroxy-oxetanes to produce intermediate hemiketals that undergo oxidative fragmentation to form three-atom or four-atom ring-enlarged homoallylic or bis-homoallylic lactones; after release of the pendant free hydroxyl group, intramolecular reorganization then leads to the final, serially ring-expanded, medium-sized *n* + *m* + *p* lactones.

In a seminal report on oxetane opening by cyclohexanone imine salts, Hudrlik and Wan indicated that cyclohexanone enolate failed to open oxetane, even in the presence of

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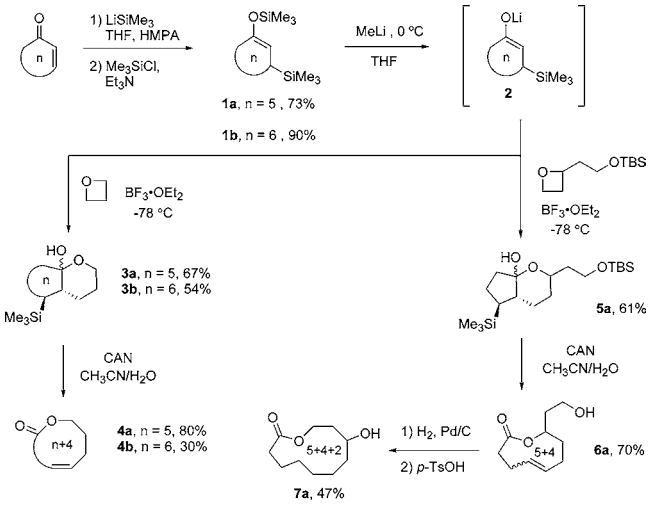
10.1021/ol051854x CCC: $30.25
Published on Web 08/17/2005

aluminum and boron Lewis acids.[7] Now we have found that boron trifluoride-etherate does in fact assist rapid oxetane opening by β-silyl cycloalkanone enolates **2** at low temperature in THF solvent to give γ-hydroxysilane intermediates **3a**, **3b**, and **5a** in 54−67% yields (Scheme 1). These

Scheme 1. Ketone Enolate Opening of Oxetanes Followed by Oxidative Clevage

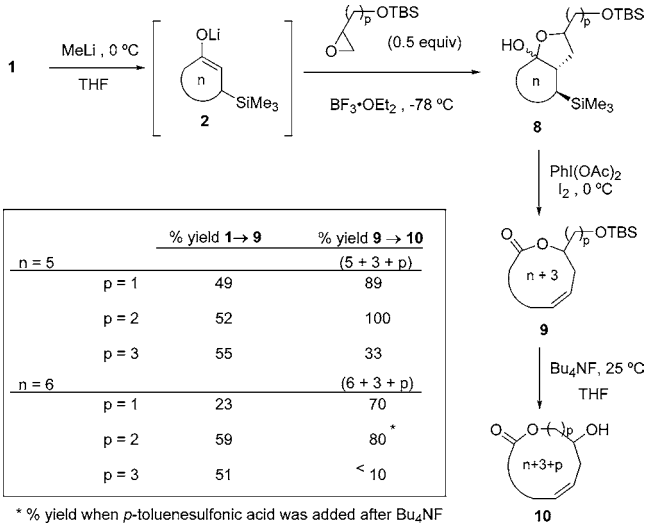


γ-hydroxysilane intermediates exist as a mixture of the hemiketal form (as shown) and the corresponding hydroxy ketone.

Oxidative cleavage of **3**, using the oxidant ceric ammonium nitrate (CAN),[8,9] produces the $n + 4$ ring-enlarged lactones **4a** and **4b** exclusively with *cis*-olefin geometry. When the oxetane carries a silyl ether protected alcohol side chain, mild and fast nucleophilic opening of the oxetane (61% yield) followed by simultaneous oxidative cleavage and silyl ether hydrolysis using CAN produces nine-membered olefinic lactone **6a** (70% yield, 1.25/1.0 *E*/*Z*). Palladium-catalyzed hydrogenation and then acid-promoted translactonization[10] finally provides 11-membered lactone **7a** via this serial $5 + 4 + 2$ ring expansion. For practical considerations, it should be noted that stock solutions of distilled enol silyl ethers **1a** and **1b** can be stored neat under inert atmosphere at −5 °C for several days without hydrolysis.

Scheme 2 illustrates silicon-mediated $n + 3 + p$ ring-enlargement reactions using functionalized epoxides to form medium-sized lactones. The following two observations are noteworthy: (1) $n + 3$ lactones **9** are formed in 49−59% overall yields from both five- and six-membered β-silyl enol ethers **1**, except for lactone **9**, $n = 6$, $p = 1$ (23% overall yield); (2) fluoride-promoted O-desilylation of the primary

Scheme 2. Translactonizations to Nine- to 12-Membered Ring Lactones

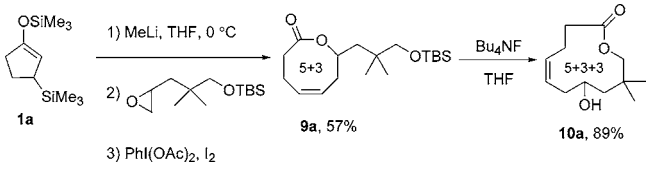


		% yield **1**→ **9**	% yield **9** → **10** (5 + 3 + p)
n = 5			
	p = 1	49	89
	p = 2	52	100
	p = 3	55	33
n = 6			(6 + 3 + p)
	p = 1	23	70
	p = 2	59	80 *
	p = 3	51	< 10

* % yield when *p*-toluenesulfonic acid was added after Bu_4NF

silyl ethers **9** liberates the corresponding primary hydroxyl group that spontaneously causes translactonization to form $n + 3 + p$ lactones **10**[11] in 70−100% yields,[12] except for **10**, $p = 3$. To assist translactonization in the difficult case of lactone **9** when $p = 3$, involving a seven-membered vs a six-membered ($p = 2$) or a five-membered ($p = 1$) tetrahedral intermediate, a *gem*-dialkyl side chain was incorporated into eight-membered lactone **9a** (Scheme 3); fluoride-induced

Scheme 3. Thorpe−Ingold Effect in Eight- to 11-Membered Ring Translactonization



desilylation led directly and spontaneously, aided by the Thorpe−Ingold effect,[13] to the desired 11-membered lactone **10a** in 51% overall yield via this serial $5 + 3 + 3$ ring-enlargement process. To improve the poor yield in the case of lactone **9**, $n = 6$, $p = 1$ (Scheme 2), we used a benzyl group instead of a TBS group for glycidol O-protection. Epoxide opening in this case proceeded more satisfactorily, giving $6 + 3$ lactone **9b** in 50% overall yield after oxidative fragmentation (Scheme 4). Thus, in only four steps from readily available 2-cyclopentenone and 2-cyclohexenone,

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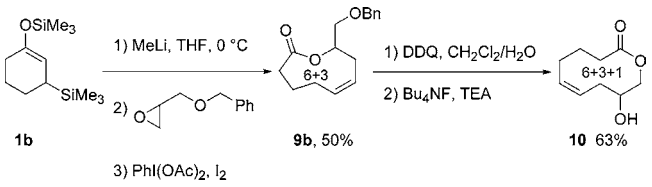
(11) Because of the nature of medium-ring lactones (ref 5), some NMR spectra may be broad due to the presence of conformational isomers.
(12) Some medium-ring lactones in Scheme 2 are a mixture of ring sizes due to incomplete translactonization and are inseparable by column chromatography. As a result, yields reported for **10**, $n = 6$, $p = 1$ and $p = 2$ reflect the actual isolated yield of $6 + 3 + p$ lactones **10** based on their ^{1}H NMR ratios.
(13) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080−1106.

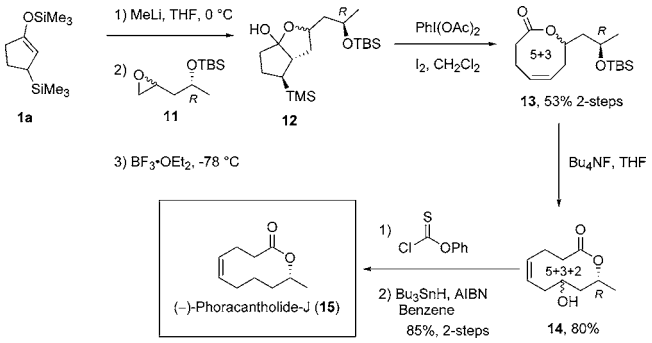
Scheme 4. 6 + 3 + 1 Ring Expansion Using Glycidyl Benzyl Ether



nine- to 12-membered, regiospecifically unsaturated, geometrically pure, *cis*-olefinic hydroxy lactones **10** are formed in good overall yields in most cases.

Phoracantholide-J (**15**) is a natural 10-membered ring olefinic lactone that is part of the defense secretion of the insect eucarypt longicorn, *Phoracantha synonyma*. This medium-sized lactone, having one stereogenic center, has been synthesized in racemic form in three different ways.[14−19] The only reported previous synthesis of (−)-phoracantholide-J (**15**) required 12 linear steps and proceeded in only 14% overall yield via initial yeast stereoselective reduction of ethyl acetoacetate.[18] Scheme 5 features our new 5 + 3 + 2 ring-

Scheme 5. Total Synthesis of (−)-Phoracantholide-J



expansion protocol for a short synthesis of (−)-phoracantholide-J (**15**). The *tert*-butyl dimethylsilyl ether **11** of the known (*R*)-4-hydroxy-1-pentene oxide[20] and cyclopentenone enol silyl ether **1a** produce hemiketal **12**, which undergoes oxidative fragmentation to afford geometrically pure *cis*-olefinic eight-membered ring lactone **13** as a diastereomeric mixture. Fluoride-induced desilylation liberates the pendant secondary alcohol that spontaneously translactonizes into 10-membered ring olefinic hydroxylactone **14**, which undergoes radical deoxygenation to yield natural (−)-phoracantholide-J (**15**, $[\alpha]^{23}$ −40.3; lit.[18] $[\alpha]^{22}$ −36.8) in six linear steps and 26% overall yield from 2-cyclopentenone.

In conclusion, we present here a four-step protocol involving three- or four-atom and subsequent one- to three-atom ring expansions of 2-cyclopentenones and 2-cyclohexenones. These $n + m + p$ sequential ring-enlargement reactions produce medium-sized lactones with a homoallylic or bis-homoallylic hydroxyl group at a specific position in the new oxygen heterocycle.[21] Incorporation of different p units in this $n + m + p$ methodology is expected to produce diverse and even more complex and useful lactones. We are actively exploring this issue as well as mechanistic understanding of the oxidative fragmentation step as part of our long-standing interest in sequential, multicomponent, ring-forming reactions.[22,23]

Acknowledgment. We thank NSF for seed support of this project and Dr. R. Larsen for a helpful discussion.

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

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(21) **Typical Gram-Scale Experimental Protocol. Formation of Hemiketal 8, $n = 5$, $p = 1$.** Silylenol-ether **1a**[4] (2.50 g, 10.9 mmol) and THF (20.0 mL) were added to a flame-dried 100 mL flask and then cooled to 0 °C. MeLi (7.01 mL, 11.3 mmol, 1.6 M in Et_2O) was added dropwise, turning the solution bright yellow. After 5 min, the flask was removed from the ice bath and cooled to −78 °C before a solution of *tert*-butyldimethylsilyl glycidol ether (1.04 g, 5.50 mmol) in THF (5.0 mL) was cannulated into the reaction. This mixture was stirred for 5 min before $BF_3{\cdot}OEt_2$ (0.693 mL, 5.50 mmol, neat) was added very slowly (1 drop/4 s) while cooling the needle with a piece of dry ice. The reaction was quenched after 30 min of stirring with phosphate buffer (15.0 mL, pH 7.0) and warmed to room temperature. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate, ∼1% TEA) to give the desired hemiketal (1.39 g, 73%) as a colorless oil. **Formation of Lactone 9, $n = 5$, $p = 1$.** Hemiketal **8**, $n = 5$, $p = 1$ (1.39 g, 4.04 mmol) was placed in a 250 mL flask with CH_2Cl_2 (100.0 mL) and cooled to 0 °C. $PhI(OAc)_2$ (1.43 g, 4.44 mmol) and then I_2 (1.02 g, 4.04 mmol, crystals) were added. The reaction immediately turned a dark purple color. The reaction was stirred for 5 h at 0 °C before quenching with a saturated solution of sodium thiosulfate. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate) to give lactone (0.73 g, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.81−5.73 (m, 2H), 4.64−4.58 (m, 1H), 3.73 (dq, $J = 10.4$, 4.8 Hz, 2H), 2.89−2.72 (m, 2H), 2.55−2.47 (m, 1H), 2.38−2.30 (m, 1H), 2.20−2.90 (m, 2H), 0.901 (s, 9H), 0.073 (d, $J = 4.4$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 176.76, 132.67, 128.13, 77.84, 64.88, 37.94, 30.59, 25.87, 18.30, −5.32, −5.35; IR (neat, cm^{-1}) 3025, 2955, 2931, 2849, 1755, 1467, 1249, 1208, 1149, 1055, 832, 779; HRMS (CI) m/z (M^+Na) calcd 293.1543 for $C_{14}H_{26}O_3SiNa^+$, found 293.1532. **Formation of Lactone 10, $n = 5$, $p = 1$.** Lactone **9**, $n = 5$, $p = 1$ (0.73 g, 2.70 mmol) was placed in a 50 mL flask with THF (15.0 mL). To this mixture was added TBAF (6.75 mL, 6.75 mmol, 1.0 M in THF) at room temperature. The reaction was quenched after 2 h by the addition of H_2O (10 mL), extracted with Et_2O (2 × 50 mL), and washed with brine (1 × 50 mL), and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (70% hexanes, 30% ethyl acetate) to give the desired lactone (0.376 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.68−5.61 (m, 2H), 4.59−4.55 (m, 1H), 4.14−4.04 (m, 2H), 2.64−2.54 (m, 2H), 2.36−2.43 (m, 1H), 2.34−2.022 (m, 3H), 1.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 174.66, 129.21, 128.11, 70.47, 68.62, 33.87, 32.12, 30.28, 29.67, 24.12; IR (neat, cm^{-1}) 3410.7, 2925.0, 2854.8, 1741.6, 1458.1, 1235.2, 1089.1, 730.2: HRMS (CI) m/z ($2M^+$Na) calcd 335.1465 for $C_{16}H_{24}O_6Na^+$, found 335.1443.

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