Pergamon

Tetrahedron Letters 41 (2000) 9655–9659

TETRAHEDRON
LETTERS

New synthetic methodology for ring expansion of *n*-sized conjugated cycloalkenones into homoallylic *n*+3 lactones: three-step synthesis of fragrant phoracantholide[†]

Gary H. Posner,* Qiang Wang, Bethany A. Halford, Jeffrey S. Elias and John P. Maxwell

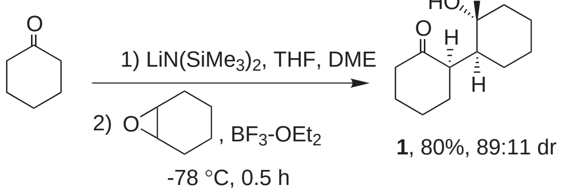
Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, MD 21218, USA

Received 31 August 2000; revised 2 October 2000; accepted 3 October 2000

Abstract

Under the influence of Lewis acidic boron trifluoride–diethyl etherate, epoxides are activated sufficiently to undergo rapid nucleophilic opening by ketone enolate ions at −78°C, forming useful γ-lactols. Application of this protocol to *n*+3 ring expansion features one-flask, multicomponent, sequential reactions. © 2000 Elsevier Science Ltd. All rights reserved.

Ketone enolate anions couple with a large variety of electrophiles, forming new carbon–carbon bonds in products of increased structural complexity.[1,2] In contrast to ester and amide enolate ions, however, ketone enolate ions do not generally open epoxides.[3] Crotti and colleagues have shown that, among diverse Lewis acids, scandium triflate activates epoxides most effectively toward intermolecular nucleophilic attack by ketone enolates, albeit requiring long reaction times (≥18 h) at room temperature.[4,5] We report here our recent discovery that boron trifluoride–diethyl etherate activates some 1-substituted and 1,2-disubstituted epoxides toward nucleophilic opening by ketone enolates under very mild reaction conditions. Examples of such syntheses of γ-hydroxy ketone products (Eq. (1)) and intermediates (Eq. (2)) are presented here, illustrating high diastereoselectivity (Eq. (1)) and a new, two-step, stereocontrolled, *n*+3 ring expansion methodology (Eq. (2)).[6]



1, 80%, 89:11 dr

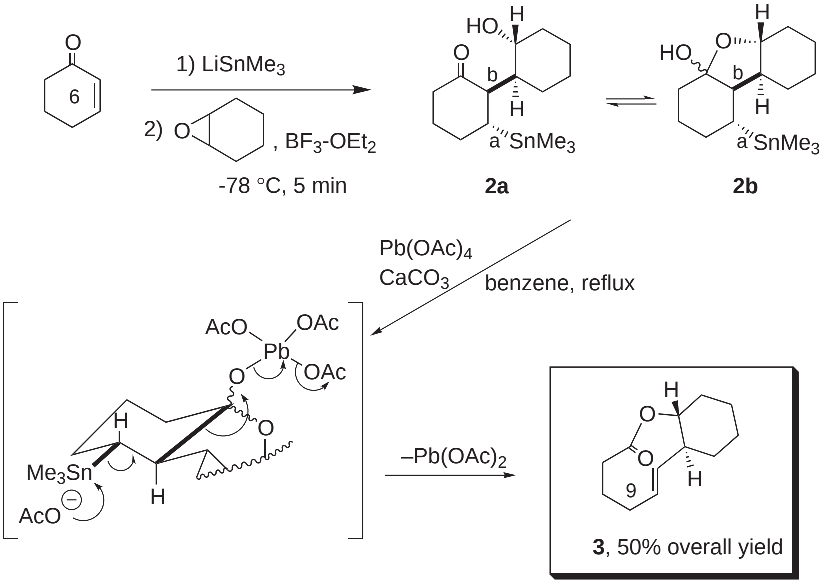
(1)

---

* Corresponding author.

[†] Dedicated to Harry Wasserman with respect, admiration, and friendship on the happy occasion of his 80th birthday.

PII: S0040-4039(00)01739-1



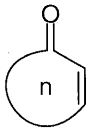
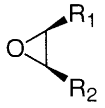
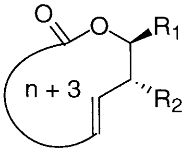
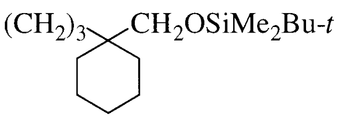
(2)

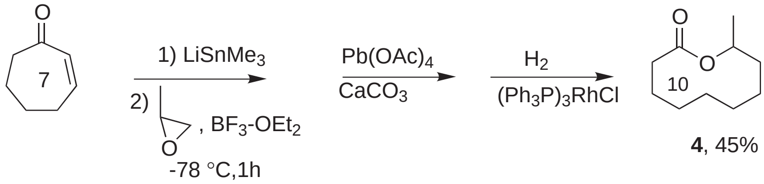
The highly diastereoselective and mild formation of γ-hydroxy ketone **1** using $BF_3{\cdot}OEt_2$ as Lewis acid (Eq. (1)) contrasts sharply with the low diastereoselectivity reported for similar ketone enolate opening of epoxides catalyzed by $Sc(OTf)_3$.[4]

We have chosen initially to establish the generality of Eq. (2) that showcases a one-flask, 3-component, sequential process in which conjugate addition of trimethyltinlithium to 2-cyclohexenone generated an enolate ion that nucleophilically opened boron trifluoride-complexed cyclohexene oxide within 5 min at −78°C; the crude mixture of γ-hydroxy ketone **2a** and the corresponding stannyl hemiketal **2b** was then fragmented by lead tetraacetate[7] into 9-membered olefinic lactone **3** in 50% overall yield. Formation of only the *E*-olefinic double bond in homoallylic product lactone **3** and the established concerted nature of the lead tetraacetate fragmentation mechanism[8] indicate that, as expected, the two new bonds a and b in hemiketal **2b** are *trans* to each other. In Table 1 are summarized results for this two-step, multicomponent ring expansion of 6- and 7-membered conjugated cycloalkenones into 3-atom enlarged, regiospecifically and stereospecifically unsaturated, 9- and 10-membered lactones. These transformations represent the synthetic equivalent of *n*+3 homologous Baeyer–Villiger oxidations[9] in which the original cycloalkenone *Z*-double bond is inverted into the *E*-double bond of the ring-enlarged lactone product. Especially valuable in the octenolide family of unsaturated lactones is that this protocol generates uniquely *E*-homoallylic lactones, whereas the corresponding *Z*-homoallylic octenolides are thermodynamically more stable.[10–12] For comparison with Crotti's protocol, we treated 2-cyclohexenone with trimethyltinlithium and then with 4-phenylbutene oxide plus $LiClO_4$ and separately plus $Sc(OTf)_3$; after lead tetraacetate fragmentation, the corresponding 9-membered olefinic lactone was isolated in only 20–25% yields (versus the 51% yield in entry 1, Table 1).

In the case of *Z*-2-cycloheptenone, our *n*+3 ring expansion protocol produced a 10-membered lactone product (Table 1, entry 7). Reduction of the lactone double bond in this case formed fragrant natural product (±)-phoracantholide[13] (**4**) in only three steps and in 45% overall yield from commercial 2-cycloheptenone (Eq. (3)). This protocol represents the shortest of the many syntheses of phoracantholide.[13] Since both enantiomers of propylene oxide are commercially available, enantiomerically pure (+)- and (−)-phoracantholide can be prepared via this synthetic methodology.

Table 1
$n+3$ Ring expansion reactions via Eq. (2)

entry	enone	epoxide		n + 3 lactone
				
	n	R$_1$	R$_2$	Yield
1	6	H	(CH$_2$)$_2$Ph	51%
2	6	H	(CH$_2$)$_2$CH=CH$_2$	49%
3	6	H	(CH$_2$)$_3$NO$_2$	52%
4	6	H	CH$_3$	54%
5	6	H	CH$_2$OPh	31%
6	6	H		40%
7	7	H	CH$_3$	50%
8	6	CH$_3$	CH$_3$	45%
9	6	CH$_2$—(CH$_2$)$_2$—CH$_2$		50%

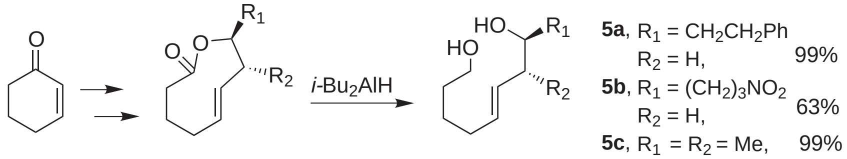


4, 45%

(3)

Variations of our protocol led to the following observations: (1) several epoxides failed to undergo this n+3 ring expansion protocol—cyclopentene oxide, cycloheptene oxide, cyclooctene oxide, 1,5-cyclooctadiene mono-epoxide, *cis* and *trans*-stilbene oxides, and styrene oxide; (2) using either tri-n-butyltinlithium or triphenyltinlithium instead of trimethyltinlithium for the initial Michael addition seriously inhibited subsequent epoxide opening; (3) performing the epoxide-opening step by adding neat $BF_3{\cdot}OEt_2$ to a mixture of the enolate plus epoxide gave similar results to those obtained by adding an ether-diluted solution of $BF_3{\cdot}OEt_2$.

The one-flask, multicomponent, domino[14] reactions described here can be used also to form regiospecifically polyfunctionalized acyclic 1,2-disubstituted alkenes. For examples, in only three steps from Z-2-cyclohexenone, E-homoallylic acyclic diols **5** were generated, with **5a** and **5b** being trifunctionalized alkenes (Eq. (4)).



5a, $R_1 = CH_2CH_2Ph$
$R_2 = H$, 99%
5b, $R_1 = (CH_2)_3NO_2$
$R_2 = H$, 63%
5c, $R_1 = R_2 = Me$, 99%

(4)

In summary, our continuing interest in one-flask, multicomponent, annulation reactions for efficient and rapid increase in molecular complexity[7,15] now includes n+3 ring expansions featuring intermolecular coupling of ketone enolates with epoxides.[16] Further applications of this methodology, including synthesis of more complex medium-ring lactones and macrolides, are being pursued.

Acknowledgements

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

References

1. Stowell, J. C. *Carbanions in Organic Synthesis*; Wiley-Interscience: New York, NY, 1979; Chapter 5.
2. Caruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, UK, 1986; Chapter 1.
3. Taylor, S. K. *Tetrahedron* **2000**, *56*, 1149–1463.
4. Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548–9552.
5. Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano, E. *Tetrahedron* **1999**, *55*, 5853–5866, and references cited therein.
6. Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH, Weinheim: Germany, 1991.
7. Posner, G. H.; Webb, K. S.; Asirvatham, E.; Jew, S.-S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, *110*, 4754–4762.
8. Nakatani, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 5335–5338.
9. Krow, G. R. *Org. React.* **1993**, *43*, 251–798.
10. Cope, A. C.; Moore, P. T.; Moore, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 3153.
11. Kling, M. R.; McNaughton-Smith, G. A.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1993**, 1593–1595.
12. Wang, T.; Chen, J.; Landrey, D. W.; Zhao, K. *Synlett* **1995**, 543–544.
13. Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1985**, *26*, 3715–3718, and references cited therein.
14. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
15. Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844.
16. A typical gram-scale experimental protocol follows: An oven-dried 250 mL round-bottomed flask equipped with a stir bar was charged with 45 mL of dry, distilled THF. Hexamethylditin (3.02 mL, 4.77 g, 14.6 mmol) was added via syringe. A yellow color developed upon the addition of methyllithium (9.66 mL of a 1.4 M solution in diethyl ether). The reaction mixture was then left to stir for 25 minutes at which point it was cooled to −78°C. Cyclohexenone (1.01 mL, 1.00 g, 10.4 mmol) was added via syringe; cyclohexene oxide (1.26 mL, 1.23 g, 12.5 mmol) was added via syringe followed by the dropwise addition of neat boron trifluoride–diethyl etherate (1.58 mL, 1.77 g, 12.5 mmol). After 5 min at −78°C, the reaction was quenched with 20 mL of distilled water, and washed twice with 100 mL of distilled water. The organic phase was dried over magnesium sulfate. The resulting crude material was reconcentrated once from 10 mL of benzene to remove moisture. An oven-dried 100 mL round-bottomed flask equipped with a stir bar was charged with calcium carbonate (1.56 g, 15.6 mmol) and lead tetraacetate (5.99 g, 13.5 mmol), equipped with a condenser, and charged with 25 mL of anhydrous benzene. This mixture was heated to reflux and a yellow color developed. The crude hydroxy ketone was dissolved in 12 mL

of anhydrous benzene and added via cannula at which point the yellow color faded and a large amount of white precipitate was formed. The reaction was left to stir at reflux for 30 minutes, quenched with 20 mL of distilled water, and diluted with 50 mL diethyl ether. The ethereal layer was washed with 150 mL of 0.3 M hydrochloric acid and 50 mL of saturated sodium bicarbonate. The ethereal layer was dried over magnesium sulfate, filtered and concentrated using rotary evaporation. This mixture was then purified using silica gel column chromatography (25% diethyl ether, 75% petroleum ether) to give 970 mg of lactone **3** as a pale yellow oil (50% yield). IR (neat) 2937 cm^{-1}, 2861, 1715 (s, C=O); ^{1}H NMR (400 MHz $CDCl_3$) δ 5.53 (quintet, $J=4$ Hz, 1H), 4.98 (dd, $J=15.6$, 9.6 Hz, 1H), 4.42 (m, 1H), 2.29–1.22 (m, 15H); ^{13}C NMR (100 MHz $CDCl_3$) δ 178.07, 134.14, 134.09, 78.92, 52.03, 33.35, 31.04, 29.25, 27.15, 26.29, 25.34, 25.18; HRMS [M^+] calculated for $C_{12}H_{18}O_2$ 194.1307, observed 194.1313. It is important to note that despite their size and molecular weight, these lactones are volatile; therefore care should be used when concentrating them.