A Versatile Preparation of 2-Methyleneoxetanes

Lisa M. Dollinger and Amy R. Howell*

Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06269-4060

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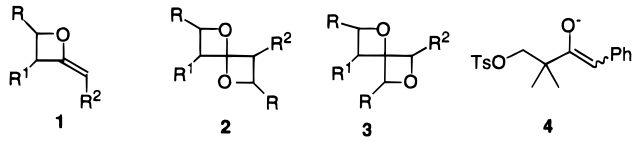
Strained, saturated heterocyclic systems have been widely employed as molecular templates in the construction of a host of organic compounds. One largely[1−4] unexplored class of strained heterocycles that should provide remarkable flexibility is the 2-alkylideneoxetanes **1**. The unique combination of functionalities—a reactive oxetane, an enol cyclic ether, and an exocyclic double bond—offers intriguing possibilities for further manipulation. Obviously, ready access to 2-alkylideneoxetanes is necessary for an exploration of their reactivity and utility.

Two approaches resulting in multiple[5] 2-alkylideneoxetanes have been previously described. The first, reported in the late 60's by Arnold[1] and Hammond,[2] utilized the Paterno-Büchi reaction with allenes (see Figure 1, path a). A very limited range of allenes was used, and further reaction to give dioxaspiroheptanes **2** and **3** was common. The other strategy, described by Hudrlik *et al.*,[6] utilized intramolecular O-alkylation of enolates (e.g., **4**). The authors found the requirement for geminal α-disubstitution to be too limiting for their purposes and did not further develop the methodology.[7] Thus, we sought a method that was straightforward, reliable, and versatile.



An elementary retrosynthetic analysis (Figure 1) of **1** would suggest two straightforward pathways to 2-alkylideneoxetanes. Path a involves a Paterno−Büchi reaction utilizing an allene as an alkene equivalent. Although, as mentioned above, this pathway is precedented,[1,2,8] it has received little attention.[9] An alternative disconnection (path b) would require a *β*-lactone and an appropriate alkylidene equivalent. In this paper, we divulge a novel application of Petasis alkylidenation chemistry[10−12] for the conversion of *β*-lactones to 2-methyleneoxetanes (**1**, R^2 = H) in moderate to good yields.

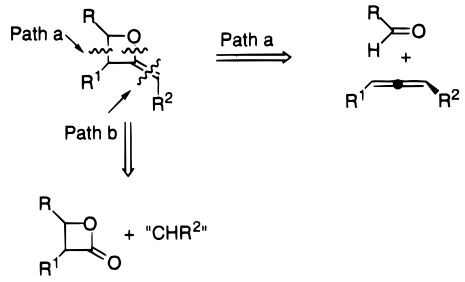
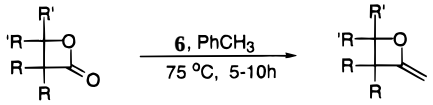


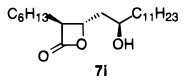
Figure 1. Retrosynthetic analysis for the preparation of 2-alkylideneoxetanes.

Table 1

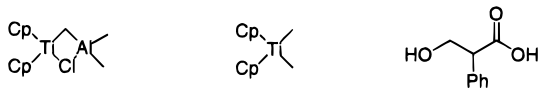


	reactant (**7**)	isolated yield (%) of **10**
a	R = CH_3; R′ = $(CH_2)_5$	67
b	R = CH_3; R′ = $C(CH_3)_3$, H[a]	50
c	R = Ph, H; R′ = H	51
d	R = Ph, CH_3; R′ = H	55
e	R = Ph, $CH_2CH{=}CH_2$; R′ = H	74
f	R = Ph, $CO(CH_2)_3CH{=}CH_2$; R′ = H	43
g	R = H; R′ = $PhCH_2CH_2$, H	32
h	R = H; R′ = H[a]	20[b]
i	see below	69

[a] These compounds are very volatile and require care when handling. [b] ^{1}H NMR of the reaction mixture indicates clean and complete conversion from reactant to product; consequently, we believe the isolated yield is a reflection of the extreme volatility of the product.



The methylenation of lactones can be readily achieved with the Tebbe reagent (**5**)[13] or by the use of dimethyltitanocene (**6**), as pioneered by Petasis and co-workers.[10−12] Interestingly, to our knowledge the methylenation of *β*-lactones has not been reported. Obviously, the acid sensitivity of *β*-lactones makes the application of these Lewis acidic reagents questionable. Further, it seems likely that a similar instability could plague the 2-methyleneoxetane products.



To investigate the conversion of *β*-lactones to 2-methyleneoxetanes, a number of *β*-lactones were prepared. *β*-Lactones **7a** and **7b** (Table 1) were synthesized as described by Schick and co-workers.[14] (±)-Tropic acid (**8**) was converted under Mitsunobu conditions to *β*-lactone **7c**. This lactone was in turn converted to lactone **7d** by deprotonation with LDA, followed by treatment with

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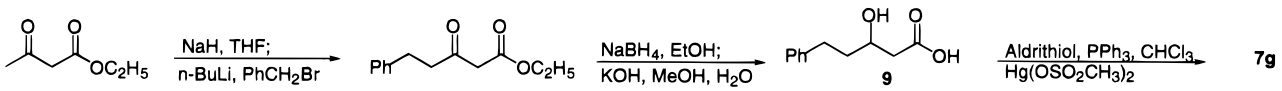
Scheme 1



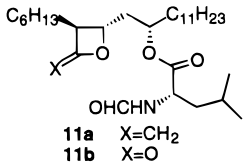
methyl iodide.[15] Lactone **7e** was obtained by the same procedure, using allyl iodide as the alkylating agent. Treatment of the enolate of **7c** with 5-hexenal, followed by oxidation with PCC, afforded lactone **7f**. Lactone **7g** was prepared[16] from 3-hydroxy-5-phenylpentanoic acid (**9**), as shown in Scheme 1. Lactone **7i**, an intermediate in a literature synthesis of tetrahydrolipstatin, was kindly provided by Hoffman LaRoche.

Our concern about the Lewis acidity of the Tebbe reagent (**5**) was well founded. Under standard conditions for Tebbe methylenation with **7c** as the substrate, proton NMR of the crude reaction mixture showed that the desired product was present, but we were unable to isolate it in significant quantity. Although we examined alternative additives (*e.g.*, basic alumina instead of pyridine) and workup conditions, the outcome was identical. On the other hand, the weaker Lewis acid, dimethyltitanocene (**6**), provided moderate to good yields of 2-methyleneoxetanes **10**,[17] as shown in Table 1.[18]

Several observations about the methylenation of β-lactones **7** and the isolation of **10** are worth noting. Previous work by Petasis[10] implied that alkylidenation proceeds *via* an intermediate that only slowly converts to product. Thus, disappearance of lactone would not necessarily be a good indicator of maximum conversion. We found, however, that for the β-lactones highest yields were realized by quenching the reaction upon consumption of the lactone. This does not preclude the formation of a long-lived intermediate, but might be indicative of product instability.[19] Toluene proved to be a superior solvent to THF for the methylenation of β-lactones. It is also interesting to note that no protection of the alcohol moiety was required in **7i**, which further illustrates the utility of the Petasis reagent. By far the most critical factor for optimum yields was the method of purification. Distillation, flash silica, Florisil, and neutral alumina all destroyed the 2-methyleneoxetanes. Basic alumina yielded the desired product, but the source and activity of the basic alumina were also crucial. Silica deactivated with triethylamine (0.5−1% in the eluting solvent) provided the most consistent results. The 2-methylene oxetanes can be stored for long periods and are stable, unless exposed to traces of acid.

Also noteworthy is the chemoselectivity of dimethyltitanocene in reactions with **7e** and **7f**. In agreement with observations by Petasis,[10] the lactone was methylenated in preference to reaction with the alkene moiety (**7e**). In contrast to prior observations of ketones being more reactive than esters, in compound **7f** the β-lactone was selectively methylenated. Although this selectivity may be a result of the hindered nature of the ketone moiety, it might also be a reflection of a greater reactivity of the β-lactone. Such selectivity would certainly have implications in protecting group strategies.

Although we are especially interested in exploring the reactivity of 2-alkylideneoxetanes, the obvious structural homology between β-lactones and 2-methyleneoxetanes has encouraged us to investigate the latter as structural isosteres of the former. This is of particular interest because, recently, several β-lactones have been identified as inhibitors of some therapeutically important serine and cysteine proteases by virtue of an enzyme-catalyzed ring-opening reaction.[20−22] Consequently, we have converted compound **10i** to 2-methyleneoxetane **11a**,[23] an analog of the pancreatic lipase inhibitor, tetrahydrolipstatin (**11b**),[24−26] and will be investigating the biological activity of it and other alkylideneoxetanes.



11a X=CH_2
11b X=O

In conclusion, we have disclosed the first reliable and straightforward preparation of 2-methyleneoxetanes in good isolated yields. Investigation of the diverse utility of this intriguing class of compounds is currently underway and will be reported in due course.

Acknowledgment. Support by donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Connecticut Research Foundation is gratefully acknowledged. We would also like to thank Bob Grubbs, Nicos Petasis, and Dominic McGrath for helpful discussions. In addition, we would like to thank Lisa Newell for preparing 3-hydroxy-5-phenylpentanoic acid (**9**) and Gan Wang for preparing lactone **7e**. We are especially grateful to Sven Taylor (Hoffman La Roche) for generously providing tetrahydrolipstatin precursor **7i**.

Supporting Information Available: Experimental procedures and spectroscopic data for all compounds (17 pages).

JO9611733

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(17) Representative experimental for the preparation of 2-methyleneoxetanes: Dimethyltitanocene (0.5 M in toluene, 19.5 mL, 9.7 mmol) and 3-phenyloxetan-2-one (**7c**) (0.96 g, 6.5 mmol) were stirred at 75 °C under N_2 in the dark. The reaction was monitored by TLC, and after the disappearance of the starting material (2−15 h) the solution was cooled and concentrated to half of its original volume. An equal volume of petroleum ether was then added, at which point a yellow precipitate formed. The mixture was passed through Celite with petroleum ether until the filtrate was colorless. After concentration, if large amounts of solid were present, the mixture was diluted with petroleum ether and filtered through Celite again. The residue was then purified by flash chromatography on silica gel (petroleum ether/ethyl acetate/triethylamine 98.5:0.5:1).

(18) All new compounds are fully characterized, and the requisite data can be found in the supporting information.

(19) Concerned about the stability of both β-lactones and 2-methyleneoxetanes at elevated temperatures, in separate experiments we heated **7c** and **10c** at 70 °C in toluene for 24 h. The lactone appeared to be unchanged; on the other hand, the oxetane showed significant decomposition.

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(23) Compound **11a** was prepared from **10i** by the method used in the synthesis of **11b** cited in ref 26. Experimental and spectral details can be found in the supporting information.

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