

6-Bromomethyl-4H-1,3-dioxin: A Versatile Bromomethyl Vinyl Ketone Equivalent for Heterocycle and Carbocycle Construction

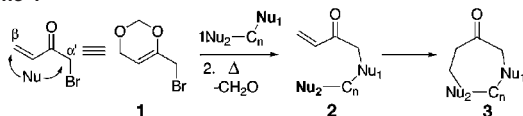
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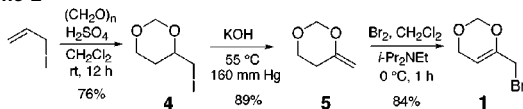
An intriguing strategy for hetero- or carbocycle synthesis involves sequential reactions of doubly nucleophilic compounds with halomethyl vinyl ketones. However, only a few examples of this type of cyclization have been reported,¹ probably because of a lack of selectivity between the β and α' sites and sensitivity of these compounds to basic reaction conditions conspire to render most strategies problematical.² These difficulties might be circumvented by employing 6-bromomethyl-4H-1,3-dioxin (**1**, Scheme 1) as an equivalent of bromomethyl vinyl ketone. Thus, the reactive allylic halide moiety of bromide **1** was expected to smoothly participate in substitution reactions and, moreover, permit the employment of highly basic nucleophiles. Subsequently, the enone functionality could be unveiled by a facile retrocycloaddition reaction of the 1,3-dioxin ring³ to afford the generic compound **2** whose remaining nucleophilic site could then be activated, if necessary, for conjugate addition to afford the desired cyclic compounds **3**. We disclose herein the realization of this methodology and document its considerable potential for the construction of natural product ring systems.

Scheme 1



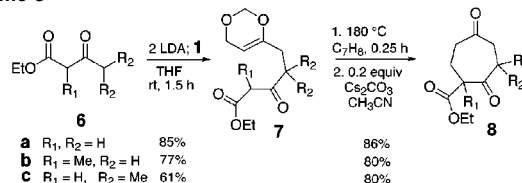
The synthesis of bromide **1** (Scheme 2) commenced with the preparation of 4-iodomethyl-1,3-dioxane (**4**) from allyl iodide following a Prins cyclization protocol reported for the analogous chloride.⁴ The iodide **4** was heated with solid KOH under reduced pressure (55 °C, 160 mmHg) to afford 4-methylene-1,3-dioxane (**5**) which distilled directly from the reaction mixture. The iodide-leaving group is critical for the success of this elimination reaction since similar treatment of 4-chloromethyl-1,3-dioxane⁴ required higher temperatures and was accompanied by comparable amounts of the endocyclic double bond isomer, 6-methyl-4H-1,3-dioxin. Bromination of the enol ether **5** in the presence of Hünig's base proceeded smoothly to provide the bromomethyl vinyl ketone equivalent **1**. The synthesis can be easily scaled to provide multigram quantities of the stable bromide **1** and, in fact, is accomplished in fewer steps than those required for the preparation of bromomethyl vinyl ketone itself.^{1c}

Scheme 2



We first examined the reactions of Weiler β -ketoesters dianions⁵ with bromide **1** (Scheme 3). Indeed, several β -ketoesters **6** cleanly afforded the desired alkylation products **7**. While the retrocycloaddition reactions of the dioxins **7** proceed at an acceptable rate in

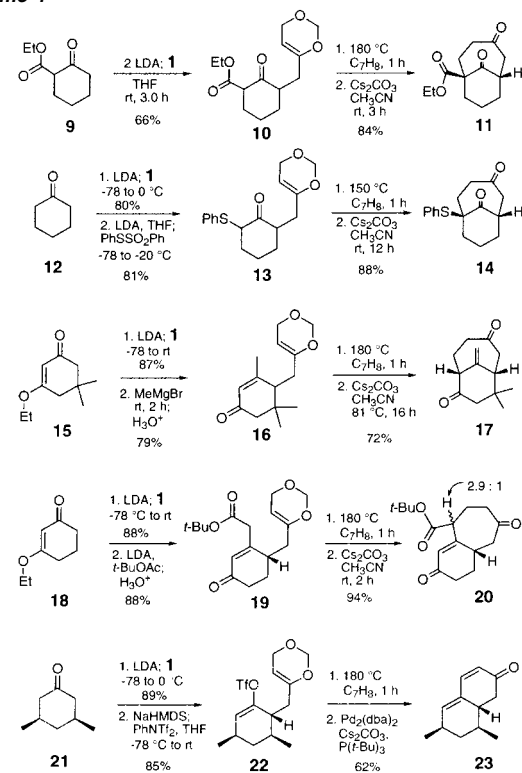
Scheme 3



refluxing toluene to give the corresponding enones (12 h), products requiring no chromatographic purification were obtained by performing the reaction at higher temperatures for shorter periods of time (toluene, sealed tube, 180 °C, 15 min). We were pleased to find that the resulting enones underwent facile 7-*endo* ring closures when subjected to reaction conditions (0.2 equiv of Cs₂CO₃, CH₃CN, rt, 1–2 h) successful for related 7-*endo* ring closures using exocyclic enolates of cyclic β -ketoesters.⁶ To the best of our knowledge, these are the first examples of *endo*-Michael additions of *endocyclic* enolates leading to seven-membered rings.⁷

We next turned our attention to annulation reactions using bromide **1** (Scheme 4). The Weiler dianion of β -ketoester **9** and the enolates of ketones **12**, **15**, **18**, and **21** all gave good yields of the corresponding alkylation products. Moreover, in several cases the 1,3-dioxin moiety of the resulting products tolerated post-

Scheme 4

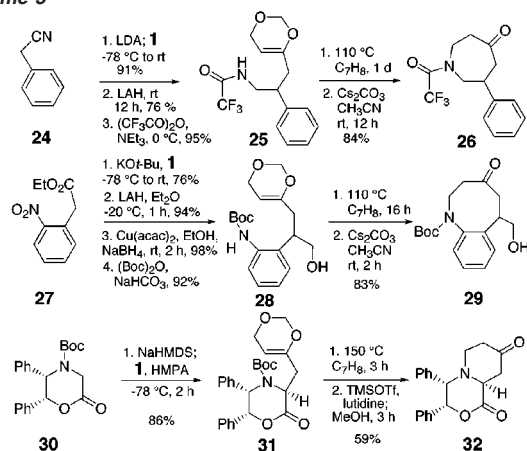


alkylation modifications such as additional enolate formation (**12** → **13** and **21** → **22**) and the nucleophilic and acidic conditions of the Stork–Danheiser enone synthesis⁸ (**15** → **16** and **18** → **19**). The sequential retrocycloaddition reactions and Michael additions of ketones **10**, **13**, and **16** all gave rise to bicyclo[4.3.1]decane-3-, 10-diones, (**11**, **14**, and **17**) the central substructure of the CP compounds.^{9a,b} Danishefsky's recent report of annulation with iodomethyl vinyl ketone and enamine derivatives of cyclohexanone served as precedent^{1b} for our complementary approach (alkylation followed by conjugate addition) to the carbon framework of these fascinating farnesyl transferase/squalene synthase inhibitors. Interestingly, the rate of these cyclizations appears to correlate with the pK_a 's of the enolate precursors. The inability to identify a conjugate addition product from the retrocycloaddition product of the *des*-phenylthio corresponding to ketone **13** is in keeping with this trend.

Fused-bicyclic products are also accessible using this annulation strategy. In contrast to **16**, the γ -methyl carbon of the retrocycloaddition product of enone **19** is activated by an ester substituent and, consequently, furnishes a diastereomeric mixture of the fused bicyclic diketo esters **20** upon completion of the annulation sequence. In addition, a six-membered, fused-ring annulation was effected by subjecting the retrocycloadduct of triflate **22** to Heck reaction conditions¹⁰ to afford the dienone **23** as a single diastereomer (see Supporting Information for diagnostic nOe's).

We have also investigated the preparation of nitrogen-containing heterocycles by the general strategy outlined in Scheme 1. To that end, the alkylation of the carbanion derivatives of nitrile **24**, ester **27**, and the Williams lactone **30**¹¹ with bromide **1** all proceeded uneventfully and furnished the expected dioxin-containing products **25**, **28**, and **31**, respectively, in excellent yield (Scheme 5). As

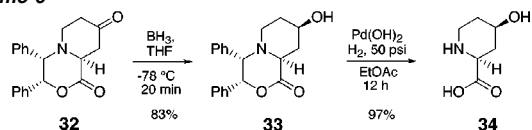
Scheme 5



before, the dioxin moiety survived subsequent manipulation of the nitrile **24** and ester **27** alkylation products to arrive at the desired cyclization precursors, trifluoroacetamide **25** and carbamate **28**, respectively. The retrocycloaddition of these compounds was best accomplished at temperatures lower than those previously utilized, although the subsequent Michael additions could be effected using the same conditions employed for the carbon nucleophiles (Schemes 3 and 4). It should be noted that benzazocines related to **29** have been the object of considerable synthetic activity^{9c} since they have been prepared en route to the antitumor compound FR-900482^{9d} (cf. ring-opened tautomeric ketohydroxylamine form).

Subjecting of the retrocycloaddition product of lactone **31** to conditions introduced by Ohfuné¹² for removal of the Boc group led to concomitant conjugate addition of the secondary amine generated during methanolysis of the intermediate trimethylsilyl carbamate. The carbonyl of the resulting piperidin-4-one **32** was

Scheme 6



then reduced stereoselectively (Scheme 6, BH_3 , $-78\text{ }^\circ\text{C}$) to provide only the equatorial alcohol **33**. Removal of the Williams' auxiliary by the standard hydrogenolysis protocol¹¹ then concluded a relatively concise synthesis¹³ of the naturally occurring (2*S*,4*R*)-4-hydroxypipercolic acid (**34**).

In conclusion, we have shown that readily available 6-bromo-methyl-4*H*-1,3-dioxin (**1**) constitutes a useful bromomethyl vinyl ketone equivalent. The exceptional reactivity of the allylic halide moiety of dioxin **1** allows facile substitution by a variety of nucleophiles. The 1,3-dioxin ring is sufficiently robust to permit, if necessary, further multistep transformation of the alkylation products. The potentially sensitive enone moiety can then be released under mild, thermal conditions and, once generated, smoothly participates in novel *endo*-conjugate addition reactions with both carbon and nitrogen nucleophiles.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (a) For the preparation of an indolizidine from chloromethyl vinyl ketone involving initial displacement of chloride ion by a thiolactam and subsequent conjugate addition of an enamine, see: Howard, A. S.; Katz, R. B.; Michael, J. P. *Tetrahedron Lett.* **1983**, *24*, 829. (b) For the preparation of bicyclo[4.*n*.1]alkan-3, (*n*+7)-diones from iodomethyl vinyl ketone by initial conjugate addition of an enamine followed by displacement of iodide ion by a regioisomeric enamine, see: Frontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 12721. (c) For the preparation of 3-pyrrolidinones from bromomethyl vinyl ketone involving initial displacement of bromide ion by a primary amine followed by conjugate addition of the resulting secondary amine, see: Westerlund, A.; Gras, J.-L.; Carlson, R. *Tetrahedron* **2001**, *57*, 5879.
- In contrast, the relatively stable Robinson annulation reagent, methyl vinyl ketone, possesses orthogonally reactive sites, an electrophilic β carbon and, once activated, a nucleophilic α' carbon.
- Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1988**, *110*, 1290.
- Priest, C. C.; Krishnamurti, I. *J. Am. Chem. Soc.* **1950**, *72*, 5335.
- Weiler, L.; Huckin, S. N. *Can. J. Chem.* **1974**, *52*, 2157.
- (a) Berthiaume, G.; Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5451. (b) Conjugate additions to ynones have also been reported, see: Lavallée, J.-F.; Berthiaume, G.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5455. (c) For $FeCl_3$ -mediated internal Michael additions to enones, see: Christoffers, J.; Oertling, H. *Tetrahedron* **2000**, *56*, 1339.
- For a single example of an undesired *endo*-Michael addition of an *endo* enolate leading to a seven-membered ring *exocyclic* enolate, see: (a) Tokoroyama, T.; Tsukamoto, M.; Iio, H. *Tetrahedron Lett.* **1984**, *25*, 5067. For an example of a 7-*exo*-Michael addition of an *endo* enolate, see: (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Org. Chem.* **1985**, *50*, 23.
- Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
- Dabrah T. T.; Kaneko, T.; Masselski, W., Jr.; Whipple, J. *J. Am. Chem. Soc.* **1997**, *119*, 1594. (b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1. (c) For the most recent approach and others cited therein, see: Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575. (d) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589.
- Fu, G. C.; Litke, A. F. *J. Org. Chem.* **1999**, *64*, 10.
- Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547.
- Sakaitani, M.; Ohfuné, Y. *Tetrahedron Lett.* **1985**, *26*, 5543.
- For the most recent synthesis and others cited therein, see: Agami, C.; Bisaro, F.; Comesse, S.; Guesné, S.; Kadouri-Puchot, C.; Morgentini, R. *Eur. J. Org. Chem.* **2001**, 2385.

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