Tandem Enamine Michael Additions to 4-(Mesyloxy)cyclopentenones: Bridged Tricyclic Skeletons via a Net [3 + 2] Construction[1]

G. U. Gunawardena, Atta M. Arif,† and F. G. West*

Department of Chemistry, University of Utah
Salt Lake City, Utah 84112

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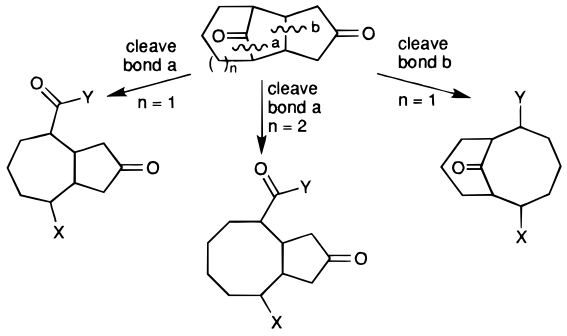
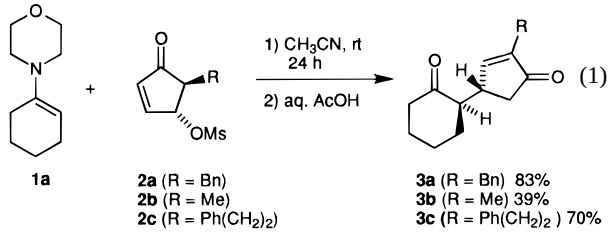
Biologically important bridged or fused bicyclic systems containing medium-sized rings are found widely in nature, and development of new synthetic approaches to these skeletons continues to be an important goal.[2] We report here a new method for the direct, convergent, and stereoselective formation of tricyclo[5.3.1.$0^{2,6}$]undecan-11-ones and tricyclo[5.4.1.$0^{2,6}$]-dodecan-12-ones from 4-(mesyloxy)cyclopentenones and pyrrolidine enamines of cyclic ketones. These products may function as useful intermediates in the synthesis of several important ring systems: selective cleavage of the zero bridge or the one-carbon bridge should furnish bicyclo[5.3.1]undecanes, bicyclo[5.3.0]decanes, or bicyclo[6.3.0]undecanes (Scheme 1).[3] The one-pot process described here is equivalent to α,α′-alkylation of an enamine by both enone double bonds of a substituted cyclopentadienone, and functions as a [3 + 2],[4] as well as a formal [5 + 2] or [6 + 2] construction.

We have found that 4-(mesyloxy)cyclopentenones undergo vicinal substitution with heteroatom nucleophiles and malonate.[5] The net result is introduction of the nucleophile at the carbon adjacent to that which bore the mesylate along with migration of the double bond to the more substituted C-4/C-5 position, presumably through an addition/elimination pathway. In an effort to expand the range of carbon nucleophiles, we were drawn to enamines as simple and well-precedented Michael donors.[6] Preliminary studies were carried out with the morpholine enamine of cyclohexanone (**1a**) and mesylates **2a**−**c**

Scheme 1



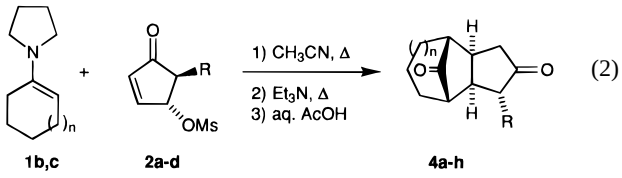
(eq 1). Reaction at ambient temperature led after aqueous



(1)

workup to "pseudocine" adducts **3a**−**c** in fair to good yield. Importantly, the product in each case was formed with complete diastereoselectivity.[7] While the relative stereochemistry of the two adjacent centers of **3** was difficult to determine directly, it is assumed to be as shown given the rigorous assignment of the related tricyclic structure **4a** (*vide infra*).

The presence of a new cyclopentenone in **3** suggested the possible intervention of a second conjugate addition in an *intramolecular* sense. When **1a** was stirred with **2a** in refluxing acetonitrile, an additional product was isolated in trace amounts and assigned tricyclic structure **4a** (eq 2). In order to facilitate



(2)

in situ enamine regeneration at the α′ position, replacement of the morpholino moiety with a pyrrolidino group was examined.[8−10] Addition of 1-(1-pyrrolidino)cyclohexene **1b** (1.5 equiv) to a solution of **2a** in acetonitrile led to rapid consumption of starting material upon heating at reflux (eq 2). Continued heating for 24 h in the presence of Et_3N (1 equiv)[11] gave after hydrolysis tricycle **4a** in 60% yield and as a single diastere-

† All inquiries regarding X-ray crystallographic data should be directed to this author.

(1) Reported in preliminary form: *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO, March 1993; American Chemical Society: Washington, DC, 1993; ORGN 83.

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(9) For conceptually related [3 + 3] annulations employing pyrrolidine enamines, see: Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.

(10) The Cook−Weiss reaction also proceeds via a [3 + 2] double-Michael annulation involving 4-hydroxycyclopentenones. See: Fu, X.; Cook, J. M. *Aldrichim. Acta* **1992**, *25*, 43.

(11) Inclusion of Et_3N was not essential for the formation of **4** but did significantly increase the rate at which it was formed and the eventual chemical yield.

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Table 1. [3 + 2] Annulation with Pyrrolidine Enamines and Mesylates **2**[a]

entry	enamine	*n*	mesylate	R	product	yield **4** (%)[b]
1	**1b**	1	**2a**	Bn	**4a**	60
2	**1b**	1	**2b**	Me	**4b**	41
3	**1b**	1	**2c**	$Ph(CH_2)_2$	**4c**	53
4	**1b**	1	**2d**	H	**4d**	40
5	**1c**	2	**2a**	Bn	**4e**	50[c]
6	**1c**	2	**2b**	Me[d]	**4f**	30
7	**1c**	2	**2c**	$Ph(CH_2)_2$	**4g**	51
8	**1c**	2	**2d**	H[d,e]	**4h**	39[f]

[a] See eq 2. Standard procedure: A solution of **1b** or **c** (1.5 equiv) in CH_3CN was added dropwise to a stirring solution of **2** in refluxing CH_3CN. After 0.5 h, Et_3N (1.1 equiv) was added, the reaction was stirred at reflux for an additional 24 h, and then aqueous AcOH was added. After a further 0.5 h at reflux, the reaction was allowed to cool and was subjected to aqueous workup and chromatography. [b] Isolated yields after chromatography. A single diastereomer was obtained unless otherwise noted. [c] A ratio of diastereomers (31:1 by ^1H NMR integration) was obtained. [d] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used in place of Et_3N. [e] The initial step was run at 0 °C for 1 h. [f] A 2:1 ratio of diastereomers was isolated.

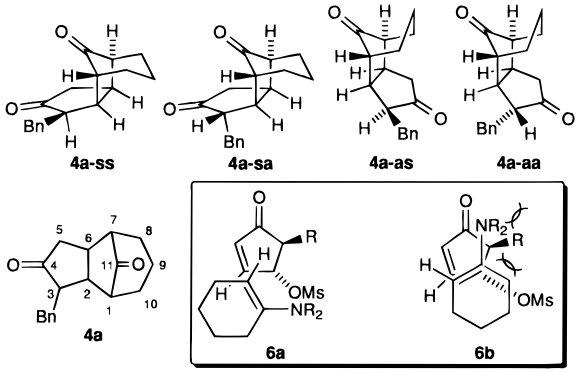
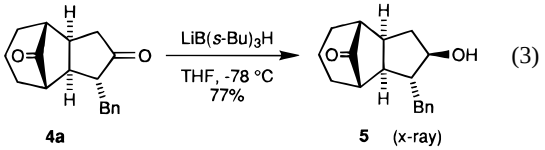


Figure 1. Possible diastereomers considered for adduct **4a**.

omer.[12] The reaction appears to be general with six- and seven-membered pyrrolidine enamines **1b**,**c** and mesylates **2a**−**d**, giving tricycles **4a**−**h** in moderate yield (Table 1).[13] *Although 4 or 5 new stereocenters are created in this process, a single diastereomer was obtained in all but two cases.*

The determination of the relative stereochemistry for adducts **4** presented a challenge. As shown for **4a** (Figure 1), each pair of bridgehead protons was presumed to have a cis relationship. However, neither the relationship of the C-2/C-6 bridgehead positions to the neighboring methine at C-3 nor that between the C-2/C-6 and the C-1/C-7 bridgeheads could be easily established. In total, four possible isomers, **4a-ss**, **4a-sa**, **4a-as**, and **4a-aa** (in which s and a refer to a syn or anti relationship between the C-2/C-1 and C-3/C-2 methine hydrogens), had to be be considered.

Stereochemical assignments were complicated by the limited chemical shift range in which most of the key methine protons fell in the ^1H NMR spectra and by their extensive vicinal and long-range coupling. To clarify the situation, derivatives of **4** suitable for X-ray crystallography were sought. Treatment of **4a** with L-Selectride led to exclusive reduction of the C-4 ketone and furnished keto alcohol **5** as a single, crystalline diastereomer (eq 3). X-ray diffraction analysis confirmed the stereochemistry



(3)

shown and established isomer **4a-sa** as the correct structure for the [3 + 2] adduct. This stereochemistry is consistent with the least-hindered antiperiplanar approach of enamine to enone as shown in "open" transition state **6a**. A synclinal orientation such as **6b** would also lead to the observed stereochemistry and is consistent with the "closed" transition state proposed for enamine additions to acyclic Michael acceptors.[9,14] However, severe nonbonding interactions between R and either the cyclohexene or pyrrolidine ring should disfavor this transition state.[15] The stereochemistry at C-3 is subject to equilibration under the basic conditions and is presumed to be thermodynamically controlled.

Spectral similarities among all tricyclic adducts support an analogous stereochemical relationship for **4b**−**h**. Isolation of **4h** as a 2:1 mixture of diastereomers is surprising. In this case, the absence of a substituent at C-5 may allow the intervention of alternative transition states to **6a**. Finally, it should be noted that choice of leaving group in the cyclopentenone partner is critical. Attempted use of 4-bromo-2-cyclopenten-1-one in place of **2d** led to little or none of the tricyclic adducts **4d** and **4h**.

We have reported a new reaction which directly joins 4-(mesyloxy)cyclopentenones and pyrrolidine enamines of cyclic ketones in a [3 + 2] sense, forming two new carbon−carbon bonds and furnishing bridged/fused tricyclic products in a single operation. The reaction typically displays high or complete stereoselectivity. Elaboration of tricyclic adducts **4** to biologically active bicyclic skeletons will be reported elsewhere.

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Supporting Information Available: Experimental procedures and physical data for **3a**−**c**, **4a**−**h**, and **5** and an ORTEP structure, tables of bond distances, bond angles, positional parameters, and torsion angles for **5** (14 pages). See any current masthead page for ordering and Internet access instructions.

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(12) For a novel photochemical route to the tricyclo[5.3.1.$0^{2,6}$]undecane skeleton, see: Subrahmanyam, G. In *Organic Photochemical Syntheses*; Srinivasan, R., Roberts, T. D., Cornelisse, J., Eds.; Wiley: New York, 1976; Vol. 2, pp 99−100.

(13) In contrast to **1b,c**, 1-(1-pyrrolidino)cyclopentene gave simple "pseudocine" substitution products analogous to **3** in moderate yields and as ca. 1:1 mixtures of diasteromers.

(14) For example, see: (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (b) For a related discussion regarding Michael additions of secondary enamines, see: Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143.

(15) The relatively polar medium employed in these annulations may also stabilize an open transition state such as **6a** relative to closed transition states.