Pseudocine Substitution via Internal Delivery. Formal Cyclopentadienone–Ketone Michael Adducts from 4-Hydroxycyclopentenones[1]

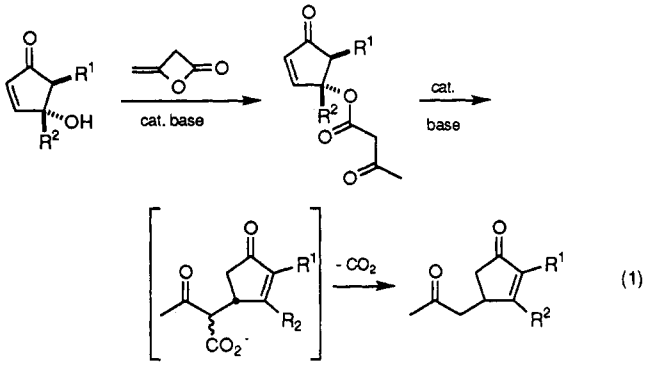
F. G. West* and Gamini U. Gunawardena

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

Received June 14, 1993®

Summary: 4-Hydroxycyclopentenones can be converted to 4-(2′-oxoalkyl)cyclopentenones in one pot upon treatment with diketene and DBU via intramolecular Michael addition of the intermediate β-keto esters.

The efficient synthesis of functionalized cyclopentanoids continues to be an important goal, given the many natural product targets containing this substructure.[2] Cyclopentenones bearing pendant keto groups are especially useful intermediates, since they could be subsequently functionalized to give modified prostaglandin side chains[3] or used for the annulation of an additional ring to the existing cyclopentane.[4] We have recently described a general route to functionalized cyclopent-2-en-1-ones involving pseudocine substitution of 4-(mesyloxy)cyclopentenones, in which heteronucleophiles or malonate are delivered vicinally to the leaving group and the cyclopentenone double bond migrates from C-2/C-3 to C-4/C-5.[5] We report here an expeditious route to 4-(2′-oxoalkyl)cyclopent-2-en-1-ones, formal ketone–cyclopentadienone Michael adducts, from readily available 4-hydroxycyclopentenones via *intramolecular* pseudocine substitution (eq 1).



(1)

Prior examples of pseudocine substitution occurred through stepwise conversion of the 4-hydroxyl to a mesylate leaving group and a presumed conjugate addition/enolate equilibration/β-elimination sequence. Given the precedent that acetate could serve as a leaving group in the elimination step,[5b] we imagined that a suitably functionalized carboxyl group could both activate the hydroxyl for

Scheme I

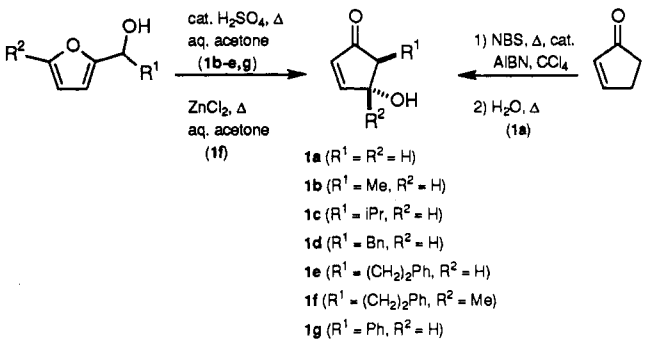
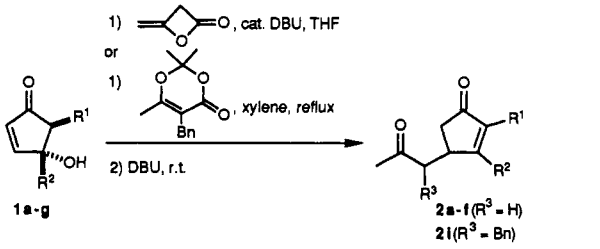


Table I. Acetoacetylation/Rearrangement of 4-Hydroxycyclopentenones



substrate	R^1	R^2	method[a]	product	yield[b] (%)
1a	H	H	A	**2a**	70
1b	Me	H	B	**2b**	45
1c	iPr	H	A	**2c**	82
1d	Bn	H	A	**2d**	81
1e	$Ph(CH_2)_2$	H	A	**2e**	76
1f	$Ph(CH_2)_2$	Me	C	**2f**	59
1g	Ph	H	D	**4g**[c]	53
1d	Bn	H	E	**2i**	51[d]
1h	$-O(CH_2)_3-$		C	**2h**	35

[a] Conditions: (A) 1 was stirred in THF (0.15 M) with DBU (0.1 equiv) and diketene (1.3 equiv) at rt. After consumption of 1, additional DBU (0.15 equiv) was added, and the reaction was stirred at rt until the intermediate acetoacetate was converted to 2. (B) As per conditions A, except 1, diketene, and DBU were initially stirred at −10 °C. After consumption of 1, additional DBU (1 equiv) was added, and the reaction was stirred at rt until the intermediate was converted to 2. (C) A solution of 1 in THF (0.2 M) was stirred at reflux with DBU (0.5 equiv) and diketene (1.5 equiv) until 1 was completely converted to 2. (D) A solution of 1 in THF (0.2 M) was stirred with Et_3N (0.3 equiv) and diketene (1.3 equiv) at rt until consumption of 1. (E) A solution of 1 in xylenes (0.7 M) was stirred with 5-benzyl-2,2,6-trimethyl-1,3-dioxin-4-one (1.05 equiv) at reflux until consumption of 1 and then cooled, diluted with THF (to a concentration of 0.15 M) and stirred with DBU (0.25 equiv) at rt until conversion of the intermediate to 2. [b] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR spectra, and combustion analysis or HRMS were obtained for all products reported. [c] See Scheme II. [d] Isolated as a 1.4:1 mixture of diastereomers.

® Abstract published in *Advance ACS Abstracts,* August 15, 1993.

(1) Presented in preliminary form: West, F. G.; Gunawardena, G. U. *Abstracts of Papers,* 205th National Meeting of the American Chemical Society, Denver, CO, March 1993; American Chemical Society: Washington, DC, 1993; ORGN 82.

(2) For reviews, see: (a) Ellison, R. A. *Synthesis* **1973**, 397. (b) Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265; **1977**, *7*, 351. (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (d) Trost, B. M. *Chem. Soc. Rev.* **1982**, 141. (e) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820. (f) Piancatelli, G. *Heterocycles* **1982**,*19*, 1775. (g) Ramaiah, M. *Synthesis* **1984**, 529. (h) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (i) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1735.

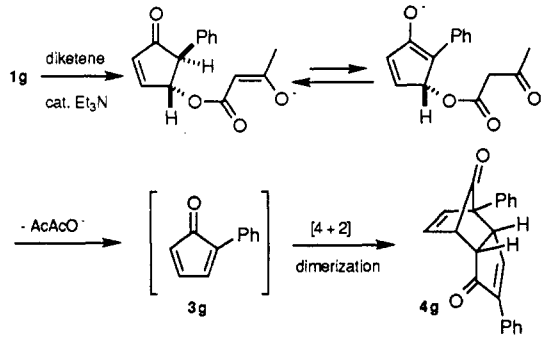
(3) (a) *Prostaglandins and Thromboxanes*, Roberts, S. M., Newton, R. F., Eds.; Butterworth Scientific: London, 1982. (b) Mitra, A. *The Synthesis of Prostaglandins*; John Wiley: New York, 1977. (c) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977.

(4) Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815. (b) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776. (c) Becker, D.; Brodsky, N. C.; Kalo, J. *J. Org. Chem.* **1978**, *43*, 2557.

(5) (a) West, F. G.; Gunawardena, G. U. *J. Org. Chem.* **1993**, *58*, 2402. (b) For a review of related studies utilizing 4-acetoxycyclopent-2-en-1-one and active methylene nucleophiles, see: Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480.

0022-3263/93/1958-5043$04.00/0

Scheme II



elimination and serve as an internal nucleophile. Since alcohols can be easily converted to β-keto esters using diketene[6] or dioxinones,[7] we chose these derivatives to test the idea of pseudocine substitution by internal delivery. The requisite 4-hydroxycyclopentenones **1b-g** could be easily prepared from substituted furyl alcohols by the method of Piancatelli (Scheme I),[8] and unsubstituted case **1a** by allylic bromination and displacement with water.[9]

Upon successive treatment with diketene/catalytic DBU and additional base, **1a-f** gave rearranged products **2a-f** in fair to excellent yield (Table I). Depending on substrate, some variation of temperature and quantity of base was necessary for optimal yields. With the exception of **1f**, omission of the second step permitted isolation of the intermediate acetoacetates. Notably, phenyl substituted substrate **1g** failed to give any of the desired product **2g**. Standard conditions led to immediate destruction, and use of catalytic Et_3N in place of DBU resulted in dimer **4g**. This presumably arises from competing elimination of the acetoacetate (Scheme II), leading to reactive cyclopentadienone **3g**, followed by the known facile Diels–Alder dimerization.[5a,10] A likely explanation for the dominance of the elimination pathway in this case is the enhanced acidity of the C-5 proton due to phenyl substitution.

A potential drawback to the reactions described above is their restriction to the introduction of three-carbon acetonyl groups. Dioxinones can serve as diketene equivalents via thermolytic extrusion of CO_2.[7] Thus, heating **1d** and 5-benzyl-2,2,6-trimethyl-1,3-dioxin-4-one[11] in refluxing xylene, followed by room temperature treatment with catalytic DBU, gave **2i** in fair yield as an inseparable mixture of diastereomers. More highly functionalized, polycyclic hydroxycyclopentenones can be readily prepared via inter- or intramolecular nucleophilic trapping of 4-pyrone-derived oxyallyl zwitterions.[12] Bicyclic ether **1h**, prepared photolytically from 2-(3′-hydroxypropyl)pyran-4-one, also underwent conversion to **2h** in modest yield under the standard diketene conditions.

In summary, readily accessible 4-hydroxycyclopentenones can be converted to rearranged 4-(2′-oxoalkyl)cyclopentenones. This transformation is carried out in one pot and two steps, using diketene or dioxinones, and the products are obtained in moderate to excellent yield. The key carbon–carbon bond-forming step occurs via intramolecular pseudocine substitution with an acetoacetate anion functioning as the internal nucleophile. Further applications of this novel class of reactions will be reported elsewhere.

Acknowledgment. We thank the National Institutes of Health (GM44720-01) for generous support of this work, along with the American Cancer Society for a Junior Faculty Research Award (F.G.W.). Mass spectrometry facilities were funded by NSF (CHE-9002690) and the University of Utah Institutional Funds Committee.

Supplementary Material Available: Experimental procedures for the preparation of substrate **1f** and rearrangement of **1a-h** and physical data for **1f**, **2a-f**, **2h-i**, and **4g** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.
(7) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431.
(8) (a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, 3555. (b) Piancatelli, G.; Scettri, A. *Ibid.* **1977**, 1131. (c) Piancatelli, G.; Scettri, A. *Tetrahedron* **1977**, *33*, 69.
(9) Baraldi, P. G.; Pollini, G. P.; Simoni, D.; Zanirato, V. *Synthesis* **1986**, 781.
(10) For a review of cyclopentadienone chemistry, see: Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65* 261.
(11) Synthesis of 5-substituted 1,3-dioxin-4-ones: Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896.
(12) (a) West, F. G.; Fisher, P. V.; Willoughby, C. A. *J. Org. Chem.* **1990**, *55*, 5936. (b) West, F. G.; Fisher, P. V.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 1595. (c) West, F. G.; Fisher, P. V.; Gunawardena, G. U.; Mitchell, S. *Tetrahedron Lett.* **1993**, *34*, 4583.