ORGANIC LETTERS

2012
Vol. 14, No. 18
4798–4801

Method for the Efficient Synthesis of Highly-Substituted Oxetan- and Azetidin-, Dihydrofuran- and Pyrrolidin-3-ones and Its Application to the Synthesis of (±)-Pseudodeflectusin

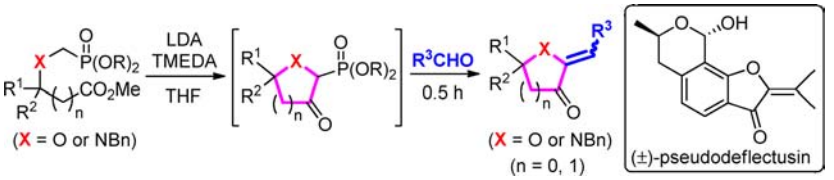
Tomohiro Maegawa, Kazuki Otake, Keiichi Hirosawa, Akihiro Goto, and Hiromichi Fujioka*

Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan

fujioka@phs.osaka-u.ac.jp

Received July 28, 2012

ABSTRACT



Highly substituted four- and five-membered heterocycles were prepared starting with *O,P*- and *N,P*-acetals by using a one-pot method involving base induced cyclization and a Horner–Wadsworth–Emmons (HWE) olefination reaction. Divergent synthesis of various heterocycles was achieved by using this method and transformations of the alkenyl group in the products of these processes were exemplified. Finally, a short and efficient synthesis of (±)-pseudodeflectusin based on the new methodology was achieved.

Because they are found in many natural products and pharmaceutical agents, methods to prepare heterocycle ring systems have remained an important theme in organic chemistry and drug discovery. Oxetan-3-ones and azetidin-3-ones are strained four-membered ring systems that comprise partial structures of a number of natural products.[1] Moreover, as has been recently demonstrated,[2] members of these families of compounds can be used in medicinal chemistry as biological equivalents of metabolically stable *gem*-dimethyl groups as well as carbonyl groups. The dihydrofuran-3-one and pyrrolidine-3-one ring systems are also found in natural products, and substances containing a 2-alkenyldihydrofuran-3-one moiety connected to an aromatic ring are members of the aurone natural product family.[3]

Despite increasing interests in oxetan- and azetidin-3-ones, the number of methods for their preparation is small, especially in contrast to the extensive number of routes that have been developed to synthesize related oxetan-2-ones and azetidin-2-ones (β-lactone and lactam).[4] Although α-diazoketone-based methods for constructing oxetan-3-ones and azetidin-3-ones are well-known, they are limited by the fact that these substrates are often difficult to handle owing to their potentially explosive nature.[1] Recently, a safer and practical procedure for synthesis of oxetan- and azetidin-3-ones that relies on the use of gold-catalyzed processes was reported.[5] However, this method cannot be

(1) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29. (b) Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.-P.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763. (c) Salgado, A.; Dejaegher, Y.; Verniest, G.; Boeykens, M.; Gauthier, C.; Lopin, C.; Tehrani, K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231. (d) Mangelinckx, S.; Boeykens, M.; Vliegen, M.; Van der Eycken, J.; De Kimpe, N. *Tetrahedron Lett.* **2005**, *46*, 525.

(2) (a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9052. (b) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Roger-Evans, M.; Müller, K. *J. Med. Chem.* **2010**, *53*, 3227.

(3) Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621.

(4) (a) Zaugg, H. E. *Org. React.* **1954**, *8*, 305. (b) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

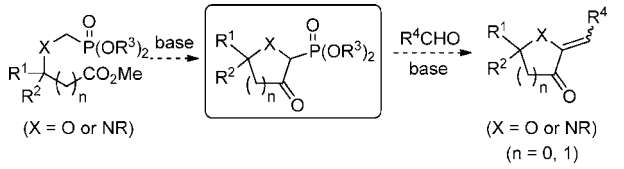
(5) (a) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (b) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236.

10.1021/ol302096j
Published on Web 08/29/2012

employed to prepare 2,4-disubstituted oxetan- and azetidin-3-ones because it utilizes alkynes as starting materials.

We have devised a new strategy for the synthesis of four- and five-membered heterocyclic compounds, which relies on the utilization of phosphonate-ester[6] cyclization reactions (Scheme 1). Below, we describe the results of an investigation to probe the viability of this strategy, which has resulted in the development of a novel approach to the synthesis of oxetan-, azetidin-, dihydrofuran- and pyrrolidin-3-ones, and a synthesis of (±)-pseudodeflectusin.

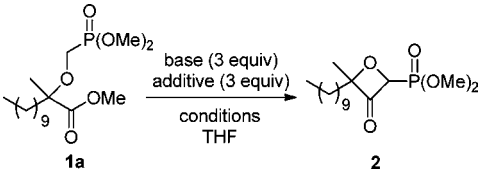
Scheme 1. Synthetic Strategy for Substituted Oxetan-, Azetidin-, Dihydrofuran- and Pyrrolidin-3-ones



In the first phase of this effort, we explored cyclization reactions of the phosphonate-ester **1a**.[7] We observed that treatment of **1a** with NaH does not result in the formation of the phosphono-oxetanone **2** (Table 1, entry 1) and that utilization of either NaHMDS or KHMDS as bases leads to formation of only trace amounts of the desired product (Table 1, entries 2 and 3). In contrast, LiHMDS and LDA are effective in promoting the cyclization reaction conducted at −78 °C, which yields product **2** in 23% and 41% respective yields (Table 1, entries 4 and 5). Increasing the reaction temperature to 0 °C (Table 1, entry 6) and including chelating agents, such as 12-crown-4, HMPA and TMEDA that increase the nucleophilicity of the anion intermediate, results in improved yields (optimal 78% yield using TMEDA, Table 1, entry 9) for the transformation of **1a** to **2** (Table 1, entries 7−9).

The results of further studies showed that **2** undergoes a HWE reaction with benzaldehyde to afford an olefination product. Specifically, treatment of **2** with LDA followed by the addition of benzaldehyde leads to formation of **3a** in 99% yield (2.6:1.0 *E*/*Z* mixture) (Scheme 2, eq 1). Importantly, the two processes converting **1a** to **3a** can be conducted using a one-pot operation (Scheme 2, eq 2). Accordingly, following treatment of **1a** with LDA and TMEDA in THF at 0 °C to form **2** (confirmed by using TLC), PhCHO is added to the mixture promoting the olefination reaction to generate **3a** in 75% yield (2.6:1.0 *E*/*Z* mixture).

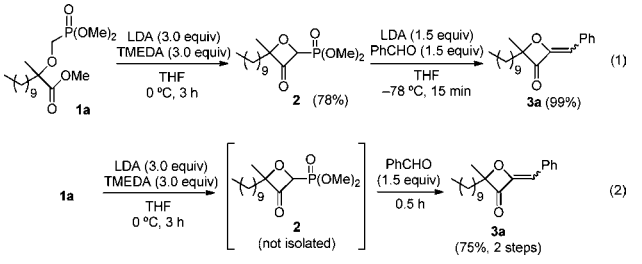
Table 1. Conditions for the Cyclization Reaction of **1a** to form Oxetan-3-one **2**



entry	base	additive	temp (°C)	*t* (h)	yield (%)[a]
1	NaH		−78 to 0	2	N.R.[b]
2	NaHMDS		−78 to 0	3	trace
3	KHMDS		−78 to 0	3	trace
4	LiHMDS		−78 to 0	3	23
5	LDA		−78 to 0	3	41
6	LDA		0	3	63
7	LDA	12-crown-4	0	3	70
8	LDA	HMPA	0	3	72
9	LDA	TMEDA	0	3	78

[a] Diastereomer ratio of **2** was 2.2:1.0 in each case. [b] No reaction.

Scheme 2. Stepwise and One-pot Conversion of **1a** to **3a**



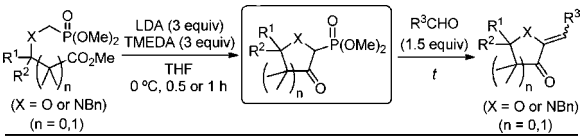
Having developed conditions for the one-pot 2-alkenyloxetan-3-one forming process, our attention next turned to an exploration of the *O*,*P*-acetal **1**[7] and aldehyde scope of process. A variety of dialkyl-substituted *O*,*P*-acetals (**1a**, **1b** and **1e**), including those containing aromatic rings were found to participate with PhCHO in the two step process to give the corresponding 2-alkenyloxetan-3-ones **3a**, **3b** and **3e** (Table 2, entries 1, 2 and 5). Interestingly, the presence of a terminal alkene moiety in **1c** does not affect the cyclization and HWE reactions (Table 2, entry 3) and the TBDPS (*tert*-butyldiphenylsilyl) group in **1d** is not altered under the reaction conditions that yield oxetan-3-one **3d** (70%) (Table 2, entry 4). The *E*/*Z* ratios of the products **3a**, **3b** and **3e** formed in respective reactions of **1a**, **1b** and **1e** ranged from 2.1:1.0 to 5.8:1.0 (Table 2, entries 1−5).[8] Moreover, aromatic aldehydes, containing electron donating and withdrawing groups, participate in the two step

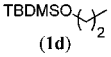
(6) We have explored novel reactivities of *O*,*P*-acetals generated from *O*,*O*-acetal and phosphine and phosphite and developed some new reactions. (a) Fujioka, H.; Goto, A.; Otake, K.; Kubo, O.; Yahata, K.; Sawama, Y.; Maegawa, T. *Chem. Commun.* **2010**, *46*, 3976. (b) Fujioka, H.; Goto, A.; Otake, K.; Kubo, O.; Sawama, Y.; Maegawa, T. *Chem. Commun.* **2011**, *47*, 9894. (c) Maegawa, T.; Otake, K.; Goto, A.; Fujioka, H. *Org. Biomol. Chem.* **2011**, *9*, 5648. (d) Fujioka, H.; Yahata, K.; Kubo, O.; Sawama, Y.; Hamada, T.; Maegawa, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 12232.(e) Goto, A.; Otake, K.; Kubo, O.; Sawama, Y.; Maegawa, T.; Fujioka, H. *Chem.—Eur. J.* **2012**, *18*, 11423.

(7) *O*,*P*-acetal **1a** was synthesized from the parent MOM ether by treatment with TMSOTf and $P(OMe)_3$. See Supporting Information for detail.

(8) Absolute *E*/*Z* stereochemistry was not determined.

Table 2. Scope of the One-pot Method for the Synthesis of 2-Alkenyl-oxetan-, azetidine-, dihydrofuran-, and pyrrolidin-3-one Starting with *O*,*P*- and *N*,*P*-acetal[a]



entry	substrate				aldehyde (R^3)	t (h)	yield (%)[b] (E/Z ratio)[c]
	n	X	R^1	R^2			
1	0	O	CH_3	$nC_{10}H_{21}$ (**1a**)	Ph	3	75 (**3a**) (2.6/1.0)
2	0	O	CH_3	$Ph(CH_2)_3$ (**1b**)	Ph	1	68 (**3b**) (2.1/1.0)
3	0	O	CH_3	 (**1c**)	Ph	1	75 (**3c**) (3.7/1.0)
4	0	O	CH_3	 (**1d**)	Ph	1	70 (**3d**) (5.8/1.0)
5	0	O	$-(CH_2)_5-$ (**1e**)		Ph	1	64 (**3e**) (5.0/1.0)
6	0	O	$-(CH_2)_5-$ (**1e**)		4-MeO C_6H_4	1	56 (**3f**) (4.2/1.0)
7	0	O	$-(CH_2)_5-$ (**1e**)		4-Cl C_6H_4	1	63 (**3g**) (4.3/1.0)
8	0	O	$-(CH_2)_5-$ (**1e**)		2-furyl	1	67 (**3h**) (3.8/1.0)
9	0	O	$-(CH_2)_5-$ (**1e**)		2-thienyl	1	68 (**3i**) (4.8/1.0)
10	0	O	$-(CH_2)_5-$ (**1e**)		CH_3CH_2	1	60 (**3j**)[d]
11	0	N Bn	CH_3	CH_3 (**4a**)	Ph	0.5	81 (**5a**) (4.8/1.0)
12	0	N Bn	$-(CH_2)_5-$ (**4b**)		Ph	0.5	80 (**5b**) (1.5/1.0)
13	0	N Bn	CH_3	CH_3 (**4a**)	4-MeO C_6H_4	0.5	80 (**5c**) (1.7/1.0)
14[e]	1	O	H	nC_9H_{19} (**6a**)	Ph	0.5	89 (**7a**) (1.9/1.0)
15[e]	1	O	H	nC_9H_{19} (**6a**)	acetone	1	63 (**7b**)
16[e]	1	O	H	Ph (**6b**)	Ph	1	92 (**7c**) (2.2/1.0)
17[e]	1	N Bn	H	nC_4H_9 (**8**)	Ph	6	70 (**9**) (3.0/1.0)

[a] Reaction conditions: *O*,*P*-acetal **1** (1 equiv), 0.5 M solution of LDA in THF-hexane (3 equiv), TMEDA (3 equiv) and aldehyde (1.5 equiv), THF (0.02 M) at 0 °C. See Supporting Information for full experimental procedure. [b] Yield starting from **1**, **4**, **6** and **8** (2 steps yield). [c] E/Z ratios are given in the parentheses and absolute stereochemistry was not determined. [d] Yield of hydrogenated product. [e] TMEDA was not present in the reaction mixture.

process that efficiently yields the corresponding products (Table 2, entries 6 and 7). Heteroaromatic aldehydes possessing furan and thiophene rings also react to afford the respective oxetan-3-one derivatives **3h** and **3i** in good yields (Table 2, entries 8 and 9). Although an aliphatic aldehyde participates in this sequence, the derived unsaturated carbonyl product is not sufficiently stable to survive column chromatographic purification. Consequently, in this case, the HWE product was immediately subjected to hydrogenation before isolation (Table 2, entry 10).

Recently, azetidin-3-one has attracted the attention of medicinal chemists because azaspiro[3.3]heptanes, to which they can be converted, serve as bioisosteres for *N* and *O* containing 6-membered ring compounds.[9] Therefore, novel methods for the synthesis of azetidin-3-ones are in great demand. In order to test the applicability of the strategy described above to the synthesis of these substances, reaction sequences involving base induced cyclizations of *N*,*P*-acetals followed by HWE olefination were explored. The results of initial studies showed that *N*,*P*-acetal **4a**[10] is transformed to the desired 2-alkenylazetidin-3-one **5a** (81%, 4.8:1.0 E/Z mixture) when sequentially treated with LDA/TMEDA and PhCHO (Table 2, entry 11). In a similar manner, the dialkyl substituted *N*,*P*-acetal **4b** reacts to afford azetidin-3-one **5b** (1.5:1.0 E/Z mixture) under the same conditions (Table 2, entry 12). Also, when 4-$MeOC_6H_4CHO$ is employed in the HWE step, the desired product **5c** is produced in high yield (Table 2, entry 13).

Applications of this strategy to the synthesis of five-membered dihydrofuran- and pyrrolidin-3-ones were also examined. As expected, *O*,*P*-acetals **6a** and **6b**[11] and *N*,*P*-acetal **8**,[11] derived from β-hydroxy and β-amino esters, were observed to undergo sequential reactions with LDA (no TMEDA) and benzaldehyde to give the corresponding five-membered heterocycles **7** and **9** in good yields (entries 14, 16 and 17). Moreover, acetone can be used in the HWE olefination step (entry 15).

The olefin moieties present in the products of these one-pot, two-step processes can be used as the starting points for a wide variety of ensuing transformations (Scheme 3). For example, **3e** was found to undergo hydrogenation (Pd/C; H_2) to afford saturated product **10a** in 92% yield (Scheme 3, eq 1). Heck reaction ($Pd(OAc)_2$, PhI, PPh_3, TBAC) of **3e** results in introduction of an aromatic substituent on the exocyclic olefin group (80%, Scheme 3, eq 2). In addition, the five-membered heterocycle **7b** is converted to epoxide **10c** in 81% yield by reaction with mCPBA (Scheme 3, eq 3).

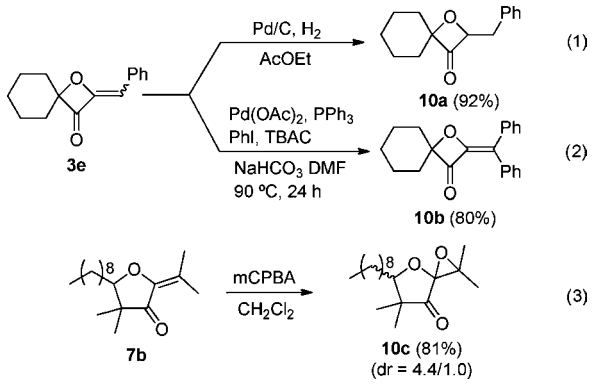
Finally, the new method was applied to a concise synthesis of (±)-pseudodeflectusin, a natural product isolated from *Aspergillus pseudodeflectus* that exhibits cytotoxicity

(9) (a) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3524. (b) Burkhard, J. A.; Guerot, C.; Knust, H.; Roger-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944.

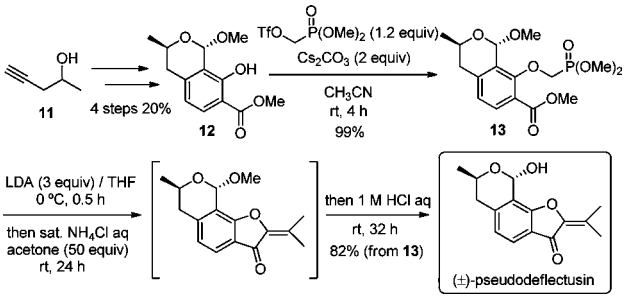
(10) *N*,*P*-acetal **3** was prepared from *N*-Bn α-aminoester and phosphonate derivative. See Supporting Information for details.

(11) Starting materials **6** and **8** were prepared according to the procedure for the synthesis of **1** and **3**. See Supporting Information for details.

Scheme 3. Transformation of **3e** and **7b**



Scheme 4. Short and Efficient Synthesis of (±)-Pseudodeflectusin



in several human cancer cell lines[12] (Scheme 4). The first synthesis of (+)-pseudodeflectusin, described by Kobayashi and his co-workers, involved in 7 steps but the yields of the last 3 steps were low to moderate.[13] Also, Takikawa and his co-workers devised an 8-step route for the preparation of the racemic natural product in 8.2% overall yield starting with homopropargylic alcohol **11**.[14] This sequence utilized a Dieckmann condensation to construct the key dihydrofuran skeleton but several steps were required to complete the preparation of the 2-alkenyl dihydrofuran-3-one.

Our sequence for the synthesis of (±)-pseudodeflectusin starts with transformation of alkyne **11** to Takikawa's intermediate **12**, which then is converted to the *O*,*P*-acetal **13**. Subjection of **13** to the one-pot cyclization−HWE sequence affords (±)-pseudodeflectusin in 82% yield. The overall route we have developed for preparation of the target involves 6-steps from **11** and takes place in a 16% overall yield.

In the studies described above, we developed a useful one-pot method for the synthesis of exocyclic olefin containing oxetan- and azetidin-3-ones, as well as dihydrofuran- and pyrrolidin-3-ones. The starting materials for these processes are *O*,*P*- and *N*,*P*-acetals that are readily available from corresponding MOM-protected α- or *β*-hydroxy esters and *N*-protected α- or *β*-amino esters.[7,10,11] Divergent transformations of the olefin moieties in the products of these reactions, including Heck coupling, hydrogenation and epoxidation reactions, take place efficiently. Finally, a concise synthesis of (±)-pseudodeflectusin was achieved by using a sequence that highlights the new method we have developed. We believe that the new strategy we have devised will be applicable to the preparation of not only oxetanes, azetidines, dihydrofurans and pyrrolidines derivatives but also other interesting heterocyclic ring systems.

Acknowledgment. This work was financially supported by the Hoansha Foundation, the Uehara Memorial Foundation, Takeda Foundation, and Grant-in-Aid for Scientific research from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan.

Supporting Information Available. General experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) Ogawa, A.; Murakami, C.; Kamisuki, S.; Kuriyama, I.; Yoshida, H.; Sugawara, F.; Mizushina, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3539.

(13) (a) Saito, F.; Kuramochi, K.; Nakazaki, A.; Mizushina, Y.; Sugawara, F.; Kobayashi, S. *Eur. J. Org. Chem.* **2006**, 4796. (b) Sato, Y.; Kuramochi, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2011**, *52*, 626.

(14) Tobe, M.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Tetrahedron* **2007**, *63*, 9333.