ORGANIC LETTERS

2009
Vol. 11, No. 22
5338−5341

A One-Pot, Base-Free Annelation Approach to α-Alkylidene-γ-butyrolactones

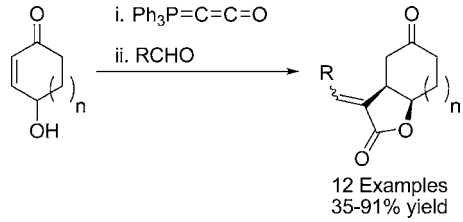
Russell R. A. Kitson,[†] Richard J. K. Taylor,*[,†] and John L. Wood[‡]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872

rjkt1@york.ac.uk

Received September 23, 2009

ABSTRACT



A novel annelation procedure has been developed for the conversion of γ-hydoxy enones into α-alkylidene-γ-butyrolactones. This one-pot method utilizes the Bestmann ylide (triphenylphosphoranylideneketene) and proceeds by way of acylation followed by an intramolecular conjugate addition/proton transfer/Wittig olefination sequence. The procedure is "base-free" and is useful for the preparation of a range of α-alkylidene-γ-butyrolactones including α-methylene-γ-butyrolactone examples, which can be particularly base-sensitive.

α-Alkylidene-γ-butyrolactones, particularly α-methylene-γ-butyrolactones, are widespread in nature and possess a range of useful biological properties.[1] We recently reported the novel approach to α-alkylidene-γ-butyrolactones outlined in Scheme 1.[2] Acylation of γ-hydoxy enones **4** using commercially available diethyl phosphonoacetic acid **5** gave diethyl phosphonoacetates **6** which, on treatment with base, underwent an intramolecular Michael addition/proton transfer sequence to generate the phosphonate anions **8** via the intermediacy of enolates **7**. Subsequent addition of an aldehyde initiated an intermolecular Horner−Wadsworth−Emmons (HWE) olefination process to give the α-alkylidene-γ-butyrolactones **9**. This telescoped intramolecular Michael/olefination (TIMO) sequence was employed by the Taylor group to prepare (+)-paeonilactone B **10**[2] and was utilized more recently by English and Williams[3] as the cornerstone of a synthesis of oleocanthal **11** in racemic form. Although highly successful, the TIMO sequence illustrated in Scheme 1 still possesses some drawbacks:

i. It did not prove possible to combine the initial acylation step with the one-pot telescoped Michael addition/HWE process.

ii. α-Alkylidene-γ-butyrolactones **9** are extremely base-sensitive; substoichiometric quantites of KO*t*-Bu were employed in the telescoped Michael addition/HWE process to maximize yields, but these conditions were obviously suboptimal (and some targets were incompatible with the basic conditions, as discussed later).

iii. Reactions using electron-deficient aromatic aldehydes as trapping agents gave inferior yields, possibly due to base-mediated Cannizzaro reactions.

In the search for an improved procedure for the overall annelation of γ-hydoxy enones **4** to produce α-alkylidene-

[†] University of York.
[‡] Colorado State University.

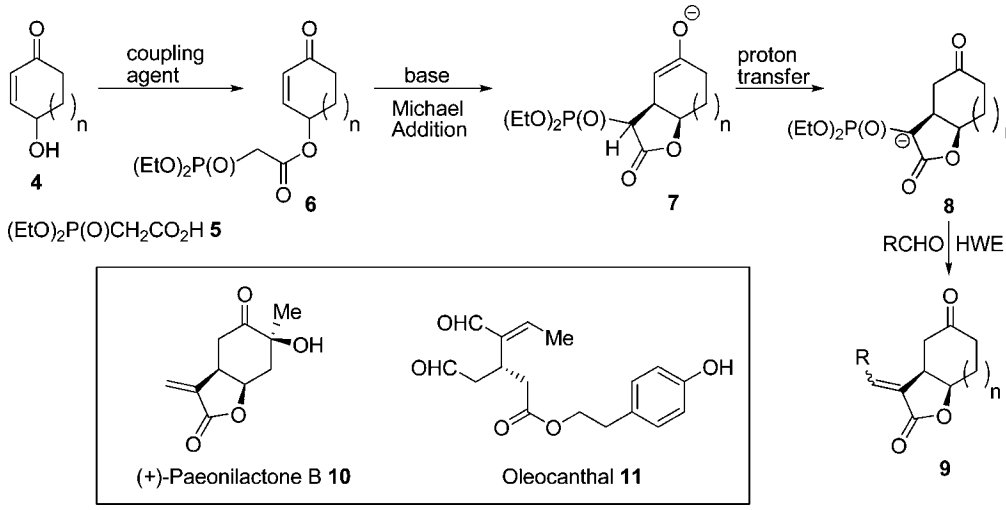
(1) For comprehensive reviews, see: (a) Hoffman, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, in press. For other recent reviews, see: (c) Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, *12*, 31. (d) Feray, L.; Bertrand, M. P. *Targets Heterocycl. Syst.* **2008**, *12*, 31.

(2) (a) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1935. (b) Edwards, M. G.; Kenworthy, M. N.; Kitson, R. R. A.; Scott, M. S.; Whitwood, A. C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2008**, 4769.

(3) English, B. J.; Williams, R. M. *Tetrahedron Lett.* **2009**, *50*, 2713.

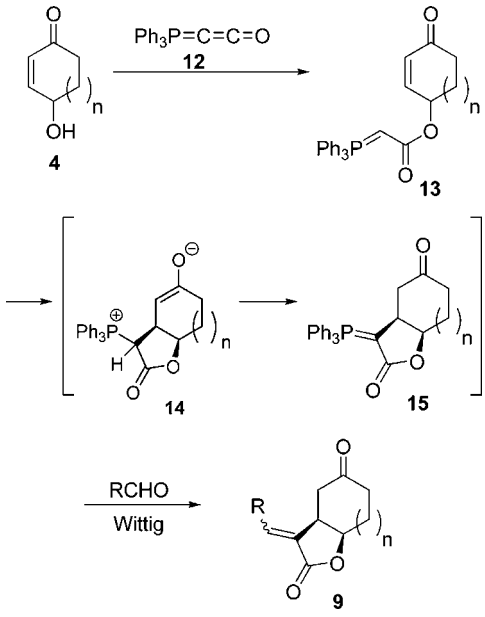
10.1021/ol902191d CCC: $40.75
Published on Web 10/27/2009

Scheme 1. TIMO Approach to α-Alkylidene-γ-butyrolactones



γ-butyrolactones **9**, preferably via a one-pot/base-free sequence, we decided to investigate the use of the Bestmann ylide (triphenylphosphoranylideneketene) **12**[4] as shown in Scheme 2. The Bestmann ylide is commercially available (Aldrich 688185-1G) or can be readily prepared from (methoxycarbonylmethylene)triphenylphosphorane using an *Organic Synthesis* procedure.[5] Reagent **12** is "remarkably stable, and solid samples can be stored for months at room temperature".[5] The Bestmann ylide is known[4−6] to react with alcohols to give the corresponding acylated phosphoranes,

Scheme 2. Bestmann's Ylide Approach to α-Alkylidene-γ-butyrolactones



and we therefore expected that treatment of γ-hydoxy enones **4** with reagent **12** would generate phosphoranes **13**. Assuming phosphoranes **13** would undergo an intramolecular conjugate addition,[7] proton transfer would be expected to occur to generate lactone phosphoranes **15** in situ. Subsequent addition of an aldehyde should result in a Wittig olefination giving α-alkylidene-γ-butyrolactones **9**. In order to evaluate the potential of the sequence, 4-hydroxy-2-cyclohexenone **16**[8] was treated with Bestmann's reagent **12** followed by paraformaldehyde, using the conditions shown in Table 1. This example was chosen because the base-sensitive nature[2] of 3-methylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione **18** would provide a challenging test for this new methodology. The process was first tested using THF as solvent (entry i), and we were delighted to observe that the acylation/conjugate addition sequence proceeded as planned and was complete in ca. 15 h (TLC analysis);[10] addition of paraformaldehyde then produced dione **18** in 78% yield. In an attempt to accelerate the acylation/conjugate addition sequence, a range of different solvents were explored; ethereal solvents proved to be optimum, and temperatures of approximately 65 °C and over were critical for the conjugate addition to occur (reaction in Et_2O gave predominantly the corresponding noncyclized acrylate **19**). 1,4-Dioxane was found to be the solvent of choice in this thermal process (entry ii), giving a faster rate for the acylation/conjugate addition step (5.5 h) and an overall yield of 86% (catalysis using benzoic acid[9] allowed the reaction to be performed at rt but resulted in reduced yields). We also investigated the use of microwave irradiation, and THF proved to be the optimal solvent using this procedure (entries iii and iv); a significant acceleration

(4) (a) Bestmann, H. J.; Sandmeier, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634. (b) Bestmann, H. J.; Sandmeier, D. *Chem. Ber.* **1980**, *113*, 274.

(5) Schobert, R. *Org. Synth.* **2005**, *82*, 140.

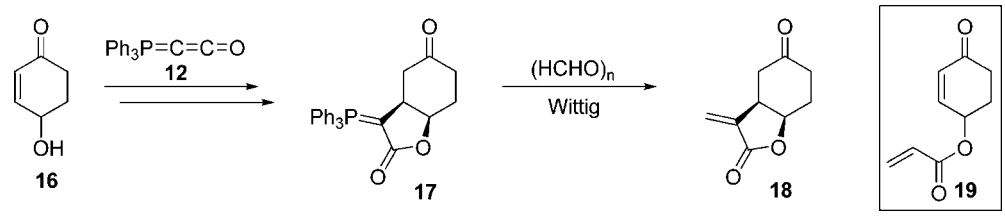
(6) For recent applications, see: Boeckman, R. K., Jr.; Song, X.; Pero, J. E. *J. Org. Chem.* **2006**, *71*, 8969, and references therein.

(7) For the conjugate addition of phosphoranes and related processes, see: Abdou, W. M.; Ganoub, N. A. F.; Mahran, M. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *66*, 79, and references therein.

(8) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.

(9) Ruchardt, C.; Panse, P.; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144.

Table 1. Optimization Studies



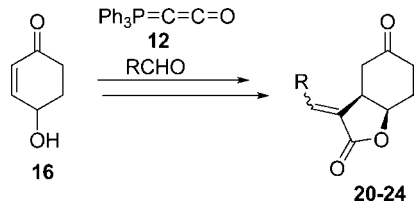
entry	solvent	acylation/conjugate addition conditions	Wittig conditions	yield **18** (%)
i	THF	Δ, 15 h	Δ, 30 min	78[a]
ii	1,4-dioxane	Δ, 5.5 h	Δ, 30 min	86[b]
iii	THF	μW (100 W, 100 °C), 1 h	μW (100 W, 100 °C), 1 h	77[c]
iv	THF	μW (100 W, 100 °C), 1 h	Δ, 30 min	86[c]

[a] Yield significantly dropped with other solvents including CH_2Cl_2, MeCN, DMF, and PhMe (trace - 52%) in Et_2O, **19** (73%) was the major product along with a small amount (5%) of **18**. [b] Addition of 5 mol % of $PhCO_2H$[9] allowed the reaction to be performed at room temperature but gave a reduced yield (40%). [c] Lower yields were observed in 1,4-dioxane.

of the acylation/conjugate addition steps was observed, but it is noteworthy that the Wittig step is less efficient in the microwave than under thermal conditions. Nevertheless, the preferred microwave/thermal procedure (entry iv) gave dione **18** in 86% yield, and the rate enhancement makes this preferable to the all-thermal process for smaller scale reactions. This annelation yield compares well with the acylation/TIMO process (68% over the two steps).[2]

With the optimization studies complete, we set about investigating the scope of the reaction sequence, initially in terms of the aldehyde component (Table 2). Thus, we first

Table 2. Scope of the Reaction Sequence[a]



entry	R	product	yield (%)[b]
i	Ph	**20**	49
ii	*p*-$MeOC_6H_4$	**21**	35[11]
iii	*p*-$NO_2C_6H_4$	**22**	67
iv	3,4,5-$(MeO)_3C_6H_2$	**23**	60
v	$Me(CH_2)_4$	**24**	71 (*E*/*Z* = 1:1)

[a] All reactions were performed in 1,4-dioxane. Unless otherwise stated, the acylation/conjugate addition was performed at reflux for 5.5 h and the Wittig olefination was performed with the aldehyde at reflux until completion (8 h to 5 days). [b] *E*/*Z* >95:<5 unless otherwise stated.

continued with 4-hydroxy-2-cyclohexenone **16** and investigated trapping with a range of aryl aldehydes (entries i−iv). Success was achieved in all cases, giving exclusively the *E*-products, but the Wittig olefination was the rate-limiting step and reactions with electron-rich aldehydes were extremely slow. It is noteworthy, however, that this base-free Bestmann ylide procedure is compatible with the use of electron-deficient aromatic aldehydes (entry iii), which could not be employed in the TIMO sequence.[2] Entry v illustrates that aliphatic aldehydes other than formaldehyde can also be utilized, although the Wittig reaction was again very slow.

Next, the scope of the reaction sequence was explored in terms of the hydroxy enone component (Table 3). First, the tertiary alcohol **25** was studied (entry i) as this proved to be a challenging substrate for the TIMO methodology[2] due to the low yield in the acylation reaction. We were delighted to observe that the Bestmann annelation sequence proceeded extremely smoothly giving α-methylene-γ-lactone **26** in 91% yield (as compared to 21% overall yield for the acylation/TIMO process[2]). Next, the cyclopentenone example **27** was studied (entry ii), and product **28** was obtained in 70% overall yield (48% via the acylation/TIMO sequence). Entry iii illustrates a process that was completely unsuccessful using the TIMO methodology; hemiacetal **29**[12] was converted into the novel monomethylene bislactone **30** in 54% unoptimized yield (the use of rt conditions was essential for success in this case; decomposition was observed on heating). Moving on to hydroxycycloheptenone **31**, product **32** was obtained efficiently (entry iv, 70%), and entry v illustrates that this new annelation procedure is applicable to acyclic systems, with hydroxyacrylate **33** giving the monocyclic product **34** in good yield. Finally, in this scoping study, the annelation of alcohol **35** was investigated and the expected δ-lactone **36** obtained in 66% yield. It should be noted that all of the bicyclic lactone products, including the 6,6-system **36**, were obtained exclusively as the *syn*-bridgehead diastereomers.

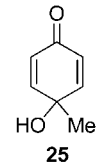
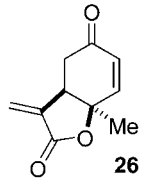
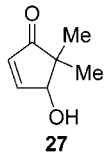
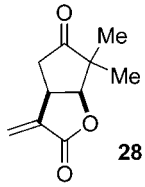
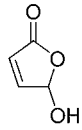
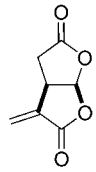
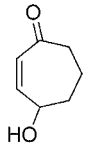
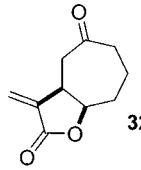
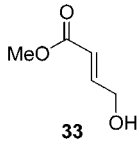
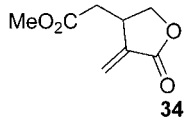
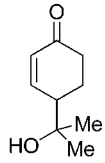
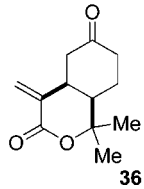
Finally, we also explored the possibility of performing the reaction in a strictly tandem sense rather than as a sequential

(10) Phosphorane lactone **17** could be obtained in near quantitative yield by working-up the reaction prior to addition of the aldehyde.

(11) Details have been deposited at the Cambridge Crystallographic Data Centre (CCDC-741196).

(12) Schroete, S. H.; Appel, R.; Brammer, R.; Schuck, G. O. *Justus Liebigs Ann. Chem.* **1966**, *697*, 42.

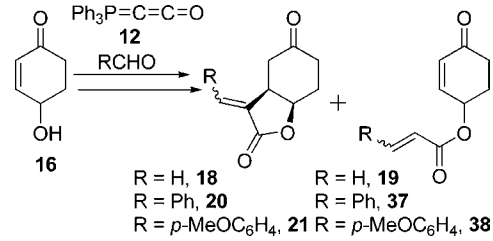
Table 3. Variation of Hydroxy Enones[a]

entry	hydroxy enone	product	yield (%)
i	 **25**	 **26**	91
ii	 **27**	 **28**	70
iii[b]	 **29**	 **30**	54
iv	 **31**	 **32**	70
v	 **33**	 **34**	68
vi[c]	 **35**	 **36**	66

[a] All reactions were performed in 1,4-dioxane. Unless otherwise stated, the acylation/conjugate addition was performed at reflux for 15 h and the Wittig olefination was performed with paraformaldehyde at reflux for 30 min. [b] Acylation/conjugate addition performed in 1,4-dioxane at rt for 5 days. [c] Acylation/conjugate addition performed in 1,4-dioxane at reflux for 2.5 days.

process, that is, adding all reagents at the outset (Table 4). Unfortunately, employing the original optimized conditions to prepare α-methylene-γ-butyrolactone **18** gave only the corresponding acrylate **19** (R = H) when paraformaldehyde was introduced from the start (entry i). However, benzoic acid (5 mol %) catalysis[9] allowed the process to be carried out at room temperature, giving the α-methylene lactone **18** (R = H) in 17% yield along with 30% of acrylate **19** (entry ii). The tandem procedure became more successful and acrylate formation was eliminated when aldehydes that are less reactive than formaldehyde were employed (entries iii and iv). With benzaldehyde, the α-arylidene-γ-butyrolactone **20** (R = Ph) was obtained in 28% yield and with *p*-methoxybenzaldehyde **21** was obtained in 39% yield (compared to 35% for the sequential process, Table 2). Importantly, in these last two processes, considerable quantities of phosphorane lactone **17** were isolated, indicating that further optimization studies could result in efficient processes (although the reaction times would need to be reduced, as well).

Table 4. Tandem Procedure[a]



entry	R	*t* (days)	yield lactone (%)	yield acrylate (%)
i	H	2	**18**, 0	**19**, 85
ii[b]	H	1	**18**, 17	**19**, 30
iii	Ph	2	**20**, 28[c]	**37**, 0
iv	*p*-$MeOC_6H_4$	5	**21**, 39[d]	**38**, 0

[a] Unless otherwise stated, the reaction was performed in 1,4-dioxane at reflux with 5 equiv of ArCHO or 10 equiv of $(HCHO)_n$. [b] Reaction was performed with 5 mol % of $PhCO_2H$ at rt.[9] [c] The corresponding sequential process gave a yield of 49%. [d] The corresponding sequential process gave a yield of 35%.

In summary, a one-pot annelation procedure has been developed for the conversion of γ-hydoxy enones into α-alkylidene-γ-butyrolactones which utilizes the Bestmann ylide (triphenylphosphoranylideneketene) and proceeds by way of acylation followed by an intramolecular conjugate addition/proton transfer/Wittig olefination sequence. The procedure is "base-free" and has been employed to prepare a range of α-methylene-γ-butyrolactones. In addition, several α-alkylidene-γ-butyrolactones have been prepared using this new methodology, although these reactions can be rather slow. Finally, preliminary studies are described which indicate the potential for a true tandem annelation procedure in which a γ-hydroxy enone, Bestmann's ylide, and an aldehyde can be directly transformed into α-alkylidene-γ-butyrolactones. We are currently optimizing the base-free Bestmann ylide annelation methodology described herein and investigating its utility for the preparation of natural products.

Acknowledgment. We thank the EPSRC for studentship support (R.R.A.K.). We are also grateful to Dr. M. G. Edwards and Dr. A. Perry (University of York) for kindly donating some of the annelation precursors, and to Dr. A. C. Whitwood (X-ray) and Dr. T. Dransfield (MS) for technical assistance.

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

OL902191D