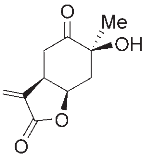
DOI: 10.1002/ange.200705329

Tandem Reactions

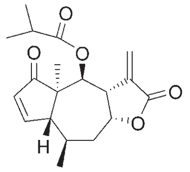
The Telescoped Intramolecular Michael/Olefination (TIMO) Approach to α-Alkylidene-γ-butyrolactones: Synthesis of (+)-Paeonilactone B**

*Michael G. Edwards, Martin N. Kenworthy, Russell R. A. Kitson, Mark S. Scott, and Richard J. K. Taylor**

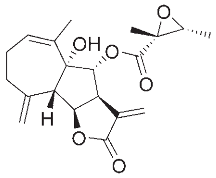
α-Alkylidene-γ-butyrolactones are widespread in nature and have diverse and potentially useful biological properties.[1] Representative examples range from the relatively simple paeonilactone B,[2] to more complex compounds such as helenalin isobutyrate[3a] and the recently isolated montahibisciolide.[3b]



Paeonilactone B[2]

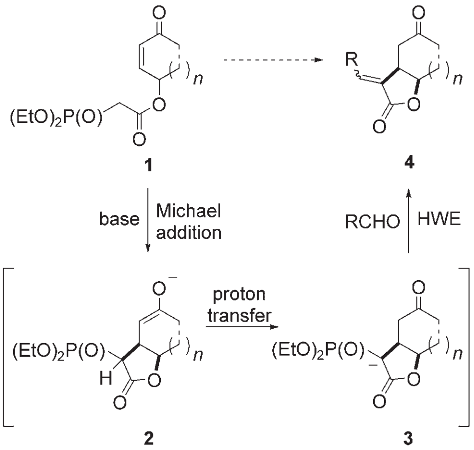


Helenalin isobutyrate[3a]



Montahibisciolide[3b]

Numerous procedures are available to prepare α-alkylidene-γ-butyrolactones; in particular, the initial construction of the lactone with subsequent methylenation is popular, but the majority of the routes are lengthy and low yielding.[1–3] As part of our growing interest in tandem or telescoped processes,[4] we designed a one-pot approach to α-alkylidene-γ-butyrolactones (Scheme 1). The key was the use of diethyl phosphonoacetate **1**, which, after deprotonation, was expected to undergo an intramolecular Michael addition[5,6] to give enolate **2**. We anticipated subsequent proton transfer to generate the more stable phosphonate anion **3** and then addition of an aldehyde to initiate an intermolecular Horner–Wadsworth–Emmons (HWE) olefination[7] to yield cyclic dicarbonyl compound **4**. In addition, we anticipated that the sequence would be *cis* selective in the formation of tetrahydrobenzofuran-2,5-dione **4** ($n=1$).



Scheme 1. Proposed TIMO approach to α-alkylidene-γ-butyrolactones.

Ketophosphonate **5** was used to assess the viability of the approach shown in Scheme 1. Compound **5** was prepared from readily available 4-hydroxy-2-cyclohexenone[8] and commercially available diethyl phosphonoacetic acid by using 2-propanephosphonic acid anhydride (T3P) as the coupling agent. When ketophosphonate **5** was treated with KO*t*Bu in THF, the expected Michael adduct **6** was obtained in 50% yield (Scheme 2). Phosphonate **6** was used to optimize the key HWE methylenation in terms of base, solvent, stoichiometry, and formaldehyde source. KO*t*Bu in THF proved to be the best base/solvent combination and paraformaldehyde was the optimal formaldehyde source. The α-methylene lactone product **7a** was highly base-sensitive, and the use of a substoichiometric quantity of base (0.95 equiv) gave product **7a** in 83% yield.

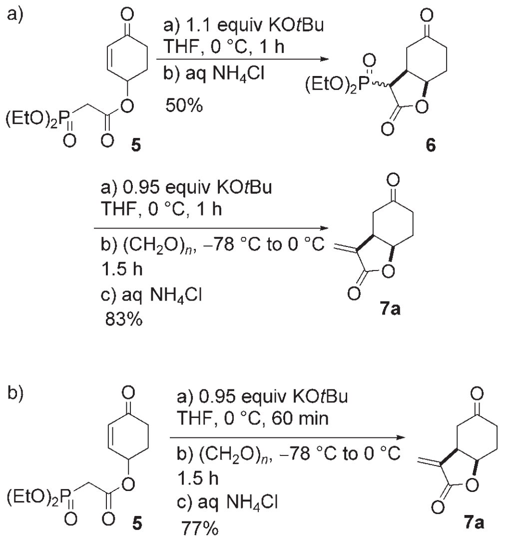
A more efficient transformation was achieved by performing a sequential one-pot process. Thus, treatment of ketophosphonate **5** with KO*t*Bu (0.95 equiv) in THF, and the addition of paraformaldehyde after 60 minutes, produced the expected α-methylene lactone **7a** in 77% overall yield. This result emphasizes the advantages of a sequential one-pot process—it avoids a complicated intermediate workup process and the overall yield is improved (77%, compared to 43% over two steps). This variant was termed a telescoped intramolecular Michael addition/HWE olefination (TIMO) process. Lactone **7a** is novel although the corresponding *trans* isomer is known.[9] The *cis* arrangement of **7a** was confirmed by obtaining an X-ray crystallographic structure.[10]

---

[*] Dr. M. G. Edwards, Dr. M. N. Kenworthy, R. R. A. Kitson, Dr. M. S. Scott, Prof. Dr. R. J. K. Taylor
Department of Chemistry
University of York
Heslington, York, YO10 5DD (U.K.)
Fax: (+44) 1904-434-523
E-mail: rjkt1@york.ac.uk

[**] We thank Elsevier Science for postdoctoral funding (M.G.E., M.N.K., and M.S.S), the EPSRC for studentship support (R.R.A.K), Archimica for a gift of T3P, and GlaxoSmithKline for additional support. We are also grateful to Dr. A. C. Whitwood (University of York, X-ray crystallography) and Dr. T. Dransfield (University of York, mass spectrometry) for technical assistance.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

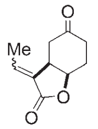
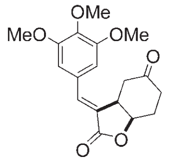
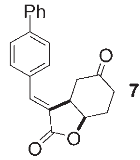
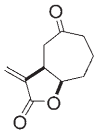
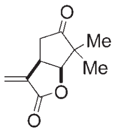
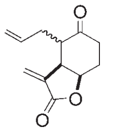
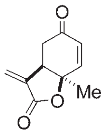


Scheme 2. a) The two-step approach to **7a**. b) The TIMO approach to **7a**.

Subsequent to our initial success, we investigated the scope of the TIMO sequence in terms of both the aldehyde and enone components (Table 1).

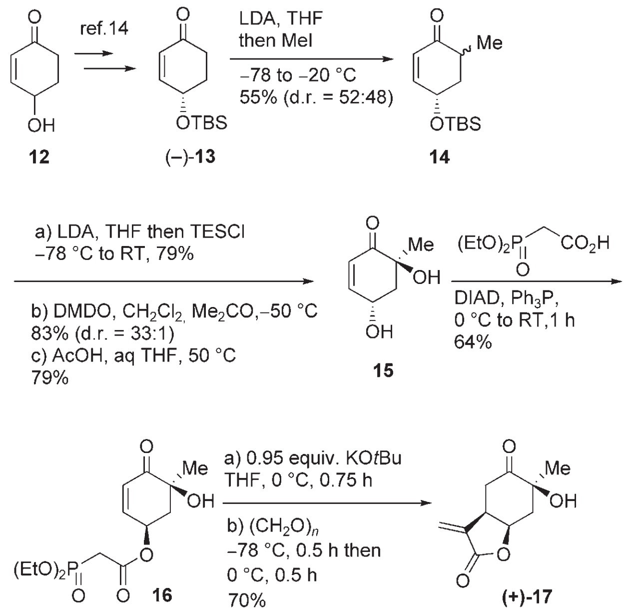
Acetaldehyde was used as the HWE partner under the optimized reaction conditions to generate ethylidene lactone **7b**, as a 1:1 mixture of *E*/*Z* isomers, in a 60 % yield (Table 1, entry 1). Aromatic aldehydes were suitable coupling partners when potassium bis(trimethylsilyl)amide (KHMDS) was used as the base. In the two examples explored (Table 1, entries 2 and 3), reasonable yields of the expected adducts **7c** and **7d** were obtained exclusively as the *E* isomers. Adduct **7d** provided crystals suitable for X-ray crystallographic analysis[10] and confirmed the *cis* ring junction and the *E* configuration of the alkene. Preliminary studies were also carried out to evaluate the scope of the γ-hydroxy enone substrate. Thus, several analogues of **5** were prepared by using similar chemistry (see the Supporting Information) and subjected to the TIMO sequence. The cycloheptanone-annelated product **8** was obtained in excellent yield, and the telescoped process was more efficient than the corresponding two-step sequence (84 % versus 22 %, Table 1, entry 4). In the cyclopentenone series (Table 1, entry 5), the 5,5-dimethyl analogue gave the expected γ-butyrolactone **9** in 52 % yield (unoptimized; the sequential process was inferior, giving the product in 31 % overall yield); compound **9** was crystalline and the structure was confirmed by X-ray crystallography.[10] To explore the effect of a substituent at the α-carbon atom of the enone, the TIMO reaction of an α-allylated enone was run under standard conditions and the expected bicyclo adduct **10** was obtained in good yield as a 3:1 diastereomeric mixture (Table 1, entry 6). Finally, a ketophosphonate derived from a tertiary alcohol underwent the TIMO sequence to give the highly functionalized bicyclic adduct **11** in 71 % yield (Table 1, entry 7).

Table 1: Scope of the TIMO reaction.[a]

Entry	Product	HWE Conditions	Yield [%]
1	 **7b**	[b]	60[e]
2[f]	 **7c**	[c]	55[g]
3[f]	 **7d**	[c]	60[g]
4	 **8**	[d]	84
5[h]	 **9**	[d]	52
6	 **10**	[d]	84[i]
7	 **11**	[b]	71

[a] Unless otherwise stated, Michael addition was performed using KO*t*Bu (0.95 equiv) for 1 h at 0 °C. [b] Reaction mixture warmed from −78 °C to 0 °C and stopped after 1 h. [c] Reaction mixture warmed from −78 °C to 0 °C over 15 h and then heated to reflux for 1 h. [d] Reaction mixture warmed from −78 °C to 0 °C and stopped after 1.5 h. [e] 1:1 *E*/*Z* mixture. [f] KHMDS (0.95 equiv) was used. [g] *E*:*Z* ratio >95:<5. [h] Michael addition performed overnight at room temperature. [i] The ratio of *anti*:*syn* diastereomers was 3:1.

Our attention turned to a natural product target to validate the utility of the TIMO sequence. Paeony root has a long history of use in Chinese and Japanese medicine for pain relief, and in 1985 paeonilactones A, B, and C were isolated from the root of *Paeonia Albiflora* Pallas.[2] Paeonilactone B (**17**)[2] was chosen as it has been prepared in racemic[12] and optically pure (+ enantiomer)[13] forms, but the lengthy routes attest to the problems associated with the preparation of such a densely functionalized molecule. The Novozyme 435 resolution procedure described by Roberts and co-workers[14] was employed to convert racemic alcohol **12** into (−)-**13** (Scheme 3). Kinetic enolate generation and subsequent methylation gave **14** as a mixture of diastereomers; the 55 % yield of **14** is modest because of the ease with which aromatization occurs in these systems. Silyl enol ether formation, subsequent oxidation by using a modified Rubottom oxidation with 2,2-dimethyldioxirane (DMDO),[15] and deprotection gave *trans*-diol **15** in an efficient and highly



Scheme 3. Synthesis of (+)-paeonilactone B [(+-**17**] by using TIMO chemistry. LDA = lithium diisopropylamide, TESCl = chlorotriethylsilane, DIAD = diisopropyl azodicarboxylate.

stereoselective three-step process (d.r. = 33:1); the use of DMDO proved to be crucial because *m*-CPBA gave a 3:1 ratio at best.

Mitsunobu coupling of alcohol **15** and diethyl phosphonoacetic acid proceeded with the desired inversion of the configuration to give the coupled product **16** in a respectable yield (notably, in the presence of the unprotected tertiary alcohol). Ketophosphonate **16** was then subjected to the TIMO reaction using KO*t*Bu in THF at 0 °C and subsequent treatment with paraformaldehyde. We were delighted that this procedure delivered (+)-paeonilactone B [(+)-**17**] in 70 % yield. The authenticity of (+)-**17** was confirmed by HRMS methods, melting points (measured: 86–87 °C, literature:[2] 88–89 °C), and optical rotation values (measured: $[\alpha]_D^{20} = +23.8\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.04\ \mathrm{g/100cm^3}$, MeOH), literature:[2] $[\alpha]_D^{20} = +23.2\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$).

The value of the telescoped intramolecular Michael addition/proton transfer/HWE olefination sequence can be gauged by the brevity of the route; [6 steps and a 13 % overall yield from the known and readily accessible enantiopure starting material (−)-**13**].

We are extending the scope of the TIMO methodology described herein and investigating its utility for the preparation of more complex targets.

Received: November 20, 2007

Keywords: α-methylene lactones · Michael addition · olefination · phosphonates · tandem reactions

---

[1] a) S.-K. Kang, K.-J. Kim, Y.-T Hong, *Angew. Chem.* **2002**, *114*, 1654–1656; *Angew. Chem. Int. Ed.* **2002**, *41*, 1584–1586; b) T. Janecki, E. Blaszczyk, K. Studzian, A. Janecka, U. Krajewska, M. Rózalski, *J. Med. Chem.* **2005**, *48*, 3516–3521; c) A. Albrecht, J. Kedzia, J. F. Koszuk, E. Warzycha, T. Janecki, *Tetrahedron Lett.* **2006**, *47*, 2353–2355; d) P. V. Ramachandran, D. Pratihar, *Org. Lett.* **2007**, *9*, 2087–2090, and references therein.

[2] T. Hayashi, T. Shinbo, M. Shimizu, M. Arisawa, N. Morita, M. Kimura, S. Matsuda, T. Kikuchi, *Tetrahedron Lett.* **1985**, *26*, 3699–3702.

[3] a) J. A. Douglas, B. M. Smallfield, E. J. Burgess, N. B. Perry, R. E. Anderson, M. H. Douglas, V. L. A. Glennie, *Planta Med.* **2004**, *70*, 166–170; b) S. Müller, R. Murillo, V. Castro, V. Brecht, I. Merfort, *J. Nat. Prod.* **2004**, *67*, 622–630, and references therein.

[4] For a review on tandem oxidation processes see: a) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, *38*, 851–869, and references therein. For general overviews on sequential and domino/tandem reactions see: b) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; d) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[5] For a review see: R. D. Little, M. R. Masjedizadeh, O. Wallquist, J. I. McLoughlin, *Org. React.* **1995**, *47*, 315–552.

[6] For intermolecular Michael additions of phosphonates see references [1b], [1c], and: a) T. Arai, H. Sasai, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 441–442. For recent publications on intramolecular Michael additions see: b) M. T. Hechavarria Fonseca, B. List, *Angew. Chem.* **2004**, *116*, 4048–4050; *Angew. Chem. Int. Ed.* **2004**, *43*, 3958–3960; c) N. Maezaki, H. Sawamoto, S. Yuyama, R. Yoshigami, T. Suzuki, M. Izumi, H. Ohishi, T. Tanaka, *J. Org. Chem.* **2004**, *69*, 6335–6340; d) J. R. Scheerer, J. F. Lawrence, G. C. Wang, D. A. Evans, *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969.

[7] For reviews see: a) J. Boutagy, R. Thomas, *Chem. Rev.* **1974**, *74*, 87–99; b) K. C. Nicolaou, M. W. Harter, J. L. Gunzner, A. Nadin, *Liebigs Ann.* **1997**, 1283–1301.

[8] S. J. Danishefsky, B. Simoneau, *J. Am. Chem. Soc.* **1989**, *111*, 2599–2604.

[9] R. K. Boeckman, Jr., M. Ramaiah, *J. Org. Chem.* **1977**, *42*, 1581–1586.

[10] CCDC 658935 (**7a**), 659261 (**7d**), and 658922 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

[11] C. Kuroda, K. Kobayashi, A. Koito, S. Anzai, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1947–1961.

[12] a) D. P. Richardson, T. E. Smith, W. W. Lin, C. N. Kiser, B. R. Mahon, *Tetrahedron Lett.* **1990**, *31*, 5973–5976; b) D. P. Richardson, P. W. Carr, J. N. Cumming, W. G. Harbison, N. D. Raoof, M. S. Sanders, E. Shin, T. E. Smith, T. H. Wintner, *Tetrahedron Lett.* **1997**, *38*, 3817–3820; c) M. Rönn, P. G. Andersson, J.-E. Bäckvall, *Acta Chem. Scand.* **1998**, *52*, 524–527; d) R. J. Boffey, W. G. Whittingham, J. D. Kilburn, *J. Chem. Soc. Perkin Trans. 1* **2001**, 487–496.

[13] a) S. Hatakeyama, M. Kawamura, E. Shimanuki, S. Takano, *Tetrahedron Lett.* **1992**, *33*, 333–336; b) S. Hatakeyama, M. Kawamura, Y. Mukugi, H. Irie, *Tetrahedron Lett.* **1995**, *36*, 267–268.

[14] J. F. Bickley, P. Evans, A. Meeks, B. S. Morgan, S. M. Roberts, *Tetrahedron: Asymmetry* **2006**, *17*, 355–362.

[15] W. Adam, L. Hadjiarapoglou, X. Wang, *Tetrahedron Lett.* **1989**, *30*, 6497–6500.