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Convergent Synthesis of Trisubstituted *Z*-Allylic Esters by Wittig−Schlosser Reaction

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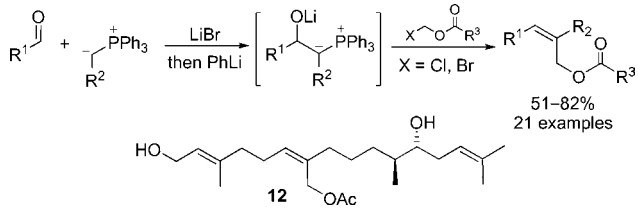
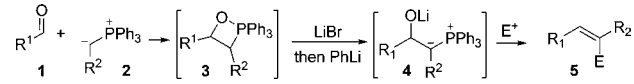
ABSTRACT



***β*-Lithiooxyphosphonium ylides, generated in situ from aldehydes and Wittig reagents, react readily with halomethyl esters to form trisubstituted *Z*-allylic esters. The methodology was applied to a total synthesis of the geranylgeraniol-derived diterpene (6*S*,7*R*,*Z*)-7-hydroxy-2-((*E*)-6-hydroxy-4-methylhex-4-enylidene)-6,10-dimethylundec-9-enyl acetate (12).**

The Wittig reaction of aldehydes **1** with phosphonium ylides **2** continues to be a popular method for alkene synthesis.[1] An important variant is the Schlosser modification,[2] which involves delaying the normal phosphine oxide elimination from the initially formed oxaphosphetane intermediate **3**, by the presence of excess soluble lithium salts and the addition of an organolithium (preferably PhLi)[3] at low temperature (Scheme 1). The lithium salts are believed to promote ring opening of the oxaphosphetane **3** to give a betaine−salt complex, which is susceptible to α-lithiation, resulting in a new ylide. Although the latter is likely comprised of complex species in solution,[1b,4] it can be represented as *β*-lithiooxyphosphonium ylide **4** for reactivity purposes. Addition of certain electrophiles to ylide **4** results in successful trapping

Scheme 1. Wittig−Schlosser Reaction



at the ylidic carbon, which is then followed by elimination of phosphine oxide. Trapping with a proton source allows access to *trans*-1,2-disubstituted alkenes **5** (E = H) from unstabilized phosphonium ylides **2** (R^2 = alkyl);[2,3] the latter would lead to *cis*-alkenes in a normal Wittig reaction. Trapping with other electrophiles constitutes a potentially powerful (triply convergent) approach to trisubstituted alkenes;[5] however, synthetically useful yields and high stereoselectivities are generally only attained for reactions with aldehydes[6] or for halogenation.[7] With excess dry paraform-

(1) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1–157. (c) Schobert, R.; Hölzel, C.; Barnickel, B. In *Science of Synthesis*; de Meijere, A., Ed.; Thieme: Stuttgart, 2010; Vol. 47a, pp 9−84.

(2) Schlosser, M.; Christmann, K. F. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 126.

(3) Wang, Q.; Deredas, D.; Huynh, C.; Schlosser, M. *Chem.−Eur. J.* **2003**, *9*, 570–574.

(4) Vedejs, E.; Meier, G. P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 56–57.

(5) Schlosser, M.; Christmann, K.-F. *Synthesis* **1969**, 38–39.

(6) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226–228, corrigendum, 3523.

(7) Hodgson, D. M.; Arif, T. *J. Am. Chem. Soc.* **2008**, *130*, 16500–16501.

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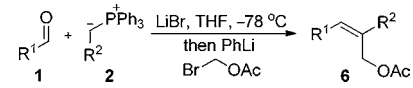
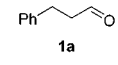
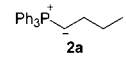
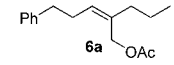
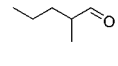
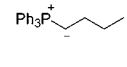
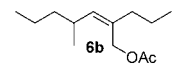
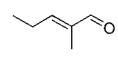
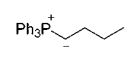
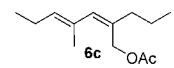
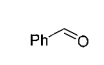
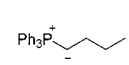
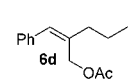
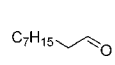
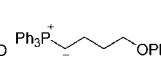
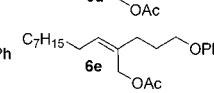
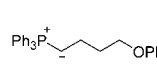
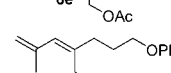
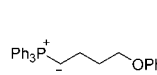
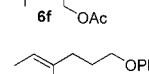
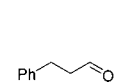
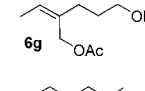
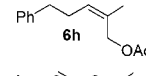
aldehyde[6] (or monomeric formaldehyde)[8] as the electrophile, the process leads to primary *Z*-allylic alcohols **5** (E = CH_2OH), and although this chemistry has found significant use in natural product synthesis[9] [mainly with ethylidene(triphenyl)phosphorane[9a,d−g]], the yields in those cases are often only moderate. On the basis that a reactive organohalide might efficiently trap the ylide **4**, we examined halomethyl esters as alternative electrophiles and report here on their promising reactivity.

Under optimal Wittig−Schlosser conditions,[3,7] we found that the β-lithiooxy ylide derived from hydrocinnamaldehyde (**1a**) and butylidene(triphenyl)phosphorane (**2a**) reacted with bromomethyl acetate[10] (1.1 equiv) to give the allylic acetate **6a** in 80% yield and excellent stereoselectivity, *Z* > 99% (Table 1, entry 1).[11,12] While an allylic ester might be required for a particular synthetic purpose (see later examples), if instead the corresponding allylic alcohol is desired,[13] then it can also be easily obtained; in an otherwise identical experiment, the crude allylic acetate **6a** was hydrolyzed with NaOMe in MeOH to give the corresponding allylic alcohol (77%) in a one-pot process. For comparison, in an otherwise identical Wittig−Schlosser reaction, but using dry paraformaldehyde as the electrophile, we obtained the allylic alcohol in 52% yield (*Z* > 99%). The scope of the allylic acetate synthesis was next examined with a range of other aldehydes **1** and phosphoranes **2** (Table 1).

Allylic acetates **6** were generally obtained in good yields and excellent *Z*-selectivities (Table 1); erosion in stereocontrol was only observed with benzaldehyde (entry 4) and also with an aliphatic aldehyde and ethylidene(triphenyl)phosphorane (entry 8). α,β-Unsaturated aldehydes proved viable substrates (entries 3, 6, and 9). It was of interest to examine the potential scope of the process for generating allylic esters other than acetates. Sterically more demanding and nonenolizable halomethyl pivaloates and benzoates would, if successful as electrophiles, provide more robustly protected allylic alcohols. Also, although bromomethyl acetate is commercially available, chloromethyl pivalate is considerably less expensive (likely due to its use in pivaloyloxymethyl ester prodrugs, of β-lactam antibiotics for example).[14] In the event, chloromethyl pivaloate and benzoate[10] displayed similar scope to bromomethyl acetate in terms of yield and stereoselectivity for allylic pivalates **7** and benzoates **8** (Figure 1). Hydrolysis of dienyl pivaloate **7e** using KO*t*-Bu/H_2O (2:1)[15] gave the corresponding dienyl alcohol (92%), previously used in a synthesis of 8-*epi*-dendrobine,[9d] and

Table 1. *Z*-Allylic Acetates **6** from β-Lithiooxyphosphonium Ylides



entry	aldehyde **1**	phosphorane **2**	allylic acetate **6**	yield, *Z*/*E*[11]
1	 **1a**	 **2a**	 **6a**	80%, >99%
2			 **6b**	73%, >99%
3			 **6c**	76%, >99%
4			 **6d**	71%, 92:8
5			 **6e**	68%, >99%
6			 **6f**	69%, >99%
7			 **6g**	64%, >99%
8			 **6h**	78%, 87:13
9			 **6i**	51%, >99%

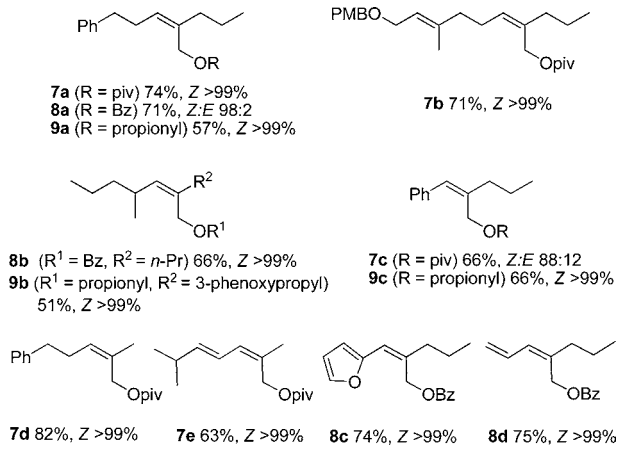


Figure 1. *Z*-Allylic pivalates **7**, benzoates **8**, and propionates **9** prepared from β-lithiooxy ylides.[11]

(8) Schlosser, M.; Coffinet, D. *Synthesis* **1971**, 380–381.

(9) For examples (target and yield for allylic alcohol indicated), see: (a) Corey, E. J.; Yamamoto, H.; Herron, D. K.; Achiwa, K. *J. Am. Chem. Soc.* **1970**, *92*, 6635−6636 [JH-I, 60%]. (b) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 6636−6637 [JH-I, 50%]. (c) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 6637−6638 [farnesol, 46%]. (d) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612−1619 [8-*epi*-dendrobine, 40%]. (e) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567−5570 [nuciferol, 42%]. (f) Liu, J.-S.; Tao, Y. *Tetrahedron* **1992**, *48*, 6193−6798 [manwuweizic acid, 54%]. (g) Fürstner, A.; Gastner, T.; Rust, J. *Synlett* **1999**, 29−32 [iricinin-4, 40%]. (h) Imamura, Y.; Takikawa, H.; Sasaki, M.; Mori, K. *Org. Biomol. Chem.* **2004**, *2*, 2236−2244 [mispyric acid, 22%].

(10) Commercially available, but was prepared from the corresponding acyl halide, paraformaldehyde and $ZnCl_2$: Sosnovsky, G.; Rao, N. U. M.; Li, S. W.; Swartz, H. M. *J. Org. Chem.* **1989**, *54*, 3667–3674.

(11) All yields reported are for chromatographically purified products. All *E*/*Z* ratios reported were determined on crude reaction mixtures by GC/MS. *E*/*Z* assignments were based on NOE studies.

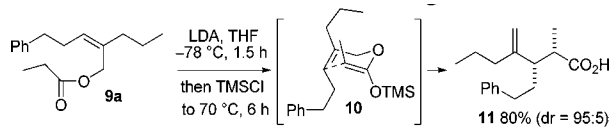
(12) Chloromethyl acetate gave the allylic acetate **6a** in 71% yield, >99% *Z*.

(13) For a review on allylic alcohols, see: Hodgson, D. M.; Humphreys, P. G. In *Science of Synthesis*; Clayden, J., Ed.; Thieme: Stuttgart, 2007; Vol. 32, pp 583−665.

provides improved access to this intermediate compared with the original Wittig−Schlosser hydroxymethylation.

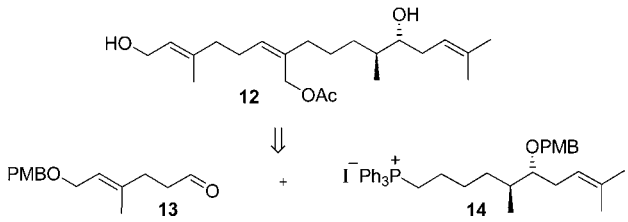
The successful generation of enolizable allylic esters higher than acetates would provide substrates directly suitable for diastereoselective (and potentially enantioselective) Ireland−Claisen rearrangements.[16] Figure 1 indicates that allylic propionates **9** could be accessed with excellent stereocontrol, albeit with, in general, slightly lower yields than found for the previously examined esters. Ireland−Claisen rearrangement of the *E*-silyl ketene acetal of allylic propionate **9a** gave γ,δ-unsaturated acid **11** in 80% yield (dr = 95:5), where the major diastereomer was assigned on the basis of the reaction preferentially proceeding through a chairlike transition state **10** (Scheme 2).[16]

Scheme 2. Ireland−Claisen Rearrangement of **9a**



To demonstrate the utility of the above allylic ester forming methodology, we focused on a synthesis of the recently reported geranylgeraniol-derived diterpene (6*S*,7*R*,*Z*)-7-hydroxy-2-((*E*)-6-hydroxy-4-methylhex-4-enylidene)-6,10-dimethylundec-9-enyl acetate (**12**, Scheme 3), which was

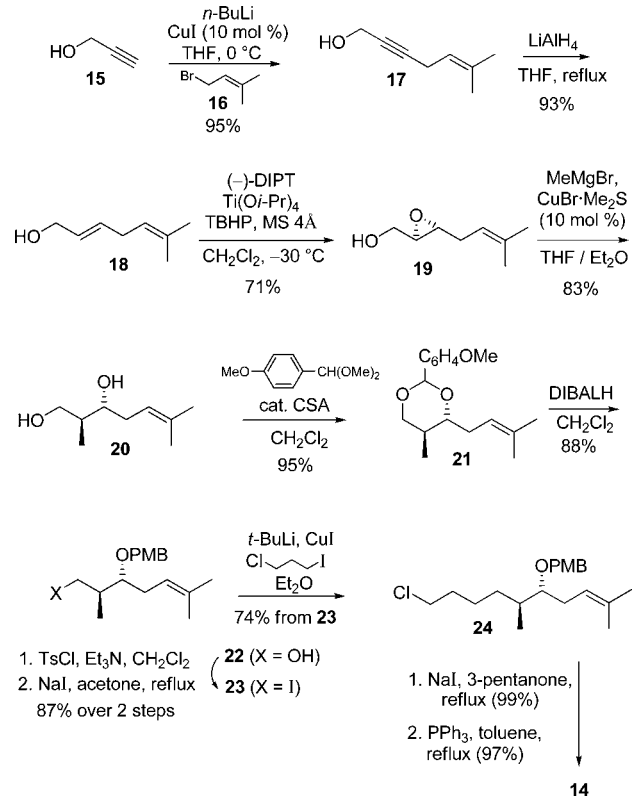
Scheme 3. Synthetic Analysis of Diterpene **12**



isolated from the seeds of *Carpesium triste*.[17] Diterpene **12** is part of a family of *Z*-allylic acetates, some of which show cytotoxic activity.

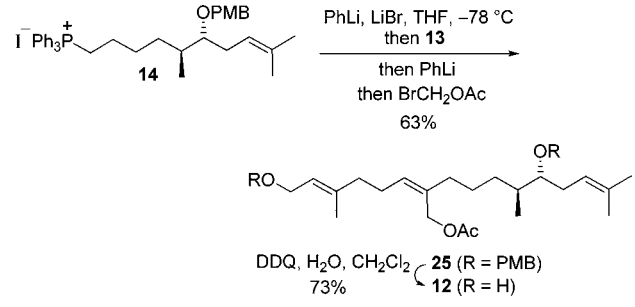
The phosphonium salt **14** for the central Wittig−Schlosser step was prepared from the known diol **20**,[18] the latter being readily available in four steps from propargyl alcohol (**15**) and prenyl bromide (**16**, Scheme 4). The originally reported modest (2:1) regioselectivity in the ring opening of epoxy

Scheme 4. Synthesis of Phosphonium Salt **14**



alcohol **19** (96% ee by chiral GC) using Me_2CuLi[18] was avoided by using MeMgBr and CuBr·Me_2S.[19] Three carbon homologation of diol-derived iodide **23** with 1-chloro-3-iodopropane using organocopper chemistry gave chloride **24** (74%), which was straightforwardly converted into phosphonium salt **14**.

Scheme 5. Completion of Synthesis of Diterpene **12**



In the key step, *Z*-allylic acetate **25** was formed in 63% yield from phosphonium salt **14**, aldehyde **13** (three steps from geraniol),[20] and bromomethyl acetate (Scheme 5).

(14) Testa, B.; Mayer, J. M. *Hydrolysis in Drug and Prodrug Metabolism*; Wiley-VCH: Weinheim, Germany, 2003.

(15) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918–920.

(16) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (b) For a review, see: Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (c) See also: Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. M. *J. Org. Chem.* **2008**, *73*, 2803–2810.

(17) Gao, X.; Lin, C.-J.; Jia, Z.-J. *J. Nat. Prod.* **2007**, *70*, 830–834.

(18) Kong, L.; Zhuang, Z.; Chen, Q.; Deng, H.; Tang, Z.; Jia, X.; Li, Y.; Zhai, H. *Tetrahedron: Asymmetry* **2007**, *18*, 451–454.

(19) Mikami, K.; Koizumi, Y.; Osawa, A.; Terada, M.; Takayama, H.; Nakagawa, K.; Okano, T. *Synlett* **1999**, 1899–1902.

(20) See Supporting Information for details.

Subsequent PMB deprotection using DDQ gave diterpene **12** (73%), with spectral and specfic rotation data in accord with that reported for the natural product.[17] Our synthesis confirms the original structural and stereochemical assignment, where the latter was based on a modified Mosher's method.

In conclusion, we have shown a new, experimentally straightforward method for the stereocontrolled formation of allylic esters by in situ trapping of β-lithiooxyphosphonium ylides with readily available halomethyl esters. Furthermore, we have demonstrated the methodology in an asymmetric synthesis of the naturally occurring diterpene **12**.

Acknowledgment. We thank the Higher Education Commission of Pakistan for studentship support (to T.A.) and Prof. Z.-J. Jia (Lanzhou) for NMR spectra of diterpene **12**.

Supporting Information Available: Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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