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Stereoselective Synthesis of β-(Hydroxymethylaryl/alkyl)-α-methylene-γ-butyrolactones

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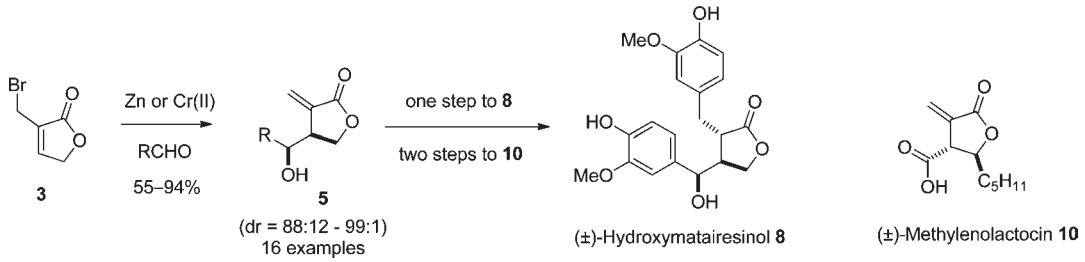
ABSTRACT



Zinc or a chromium(II) source with 3-(bromomethyl)furan-2(5*H*)-one (3) and an aldehyde gives β-(hydroxymethylaryl/alkyl)-α-methylene-γ-butyrolactones 5 in good yields and high diastereoselectivities. The methodology is demonstrated in concise syntheses of (±)-hydroxymatairesinol (8) and (±)-methylenolactocin (10) by subsequent arylboronate conjugate addition and translactonization, respectively.

The α-methylene-γ-butyrolactone motif is found in a large range of natural products, especially sesquiterpene lactones (Figure 1).[1] The presence of the motif is considered to be a major factor in the diverse biological activity observed for these natural products. Consequently, many methods have been developed to access α-methylene-γ-butyrolactones[1] for use in target synthesis and medicinal chemistry[2] programs.

However, at the outset of our studies the allylation method outlined in Scheme 1 to give such systems containing diverse β-hydroxymethyl substitution **5** had not been examined, aside from the work of Liu and co-workers to additionally γ-substituted adducts involving alkyne-derived molybdenum– or tungsten–π-allyl intermediates

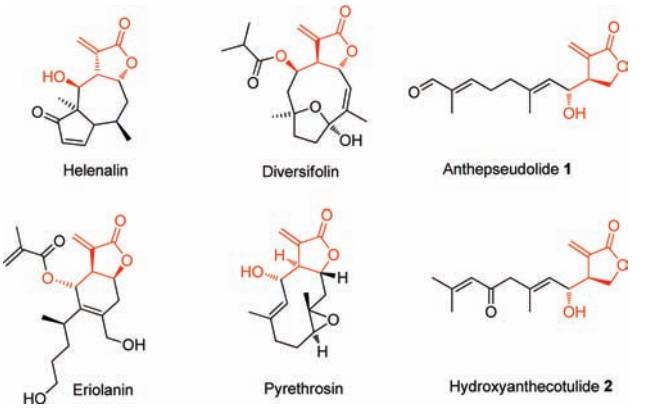


Figure 1. Representative α-methylene γ-butyrolactones.[1]

(**4**, M = MoL_n or WL_n, X = alkyl).[3,4] This substitution pattern is present in several sesquiterpene lactones (e.g., Figure 1), and the method could be of direct utility in syntheses of anthepseudolide (**1**)[5] and the antibacterial

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(1) (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451. (b) Elford, T. G.; Hall, D. G. *Synthesis* **2010**, 893–907.

(2) (a) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rózalski, M. *J. Med. Chem.* **2005**, *48*, 3516–3521. (b) Ramachandran, P. V.; Pratihar, D.; Nair, H. N. G.; Walters, M.; Smith, S.; Yip-Schneider, M. T.; Wu, H.; Schmidt, C. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6620–6623.

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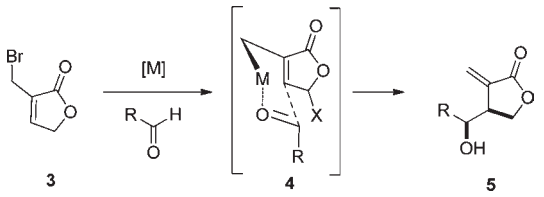
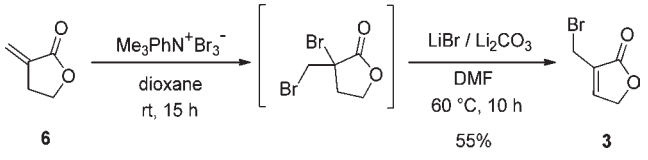
hydroxyanthecotulide (**2**)[6] and analogues.[7] We also viewed alcohols **5** as potentially versatile substrates for conjugate addition and isomerization chemistry, which could lead to other bioactive natural product classes (see later).

Scheme 1. Direct Synthesis of β-(Hydroxymethyl)-α-methylene-γ-butyrolactones **5** from Aldehydes



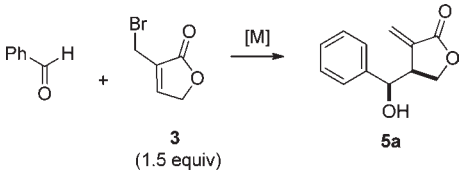
So as to investigate the above chemistry bromolactone **3**, previously accessed in six steps from γ-butyrolactone,[8] was conveniently prepared from commercially available tulipalin (**6**)[9] (Scheme 2). Bromination of **6** with phenyltrimethyl ammonium tribromide, followed by regioselective elimination using $LiBr/Li_2CO_3$ in DMF,[10] gave bromolactone **3** in 55% yield after one purification step.

Scheme 2. Synthesis of Bromolactone **3**



With bromolactone **3** in hand, Barbier-type coupling with benzaldehyde was investigated. Allylic chromium[11] or zinc[12] intermediates (Scheme 1, M = CrL_n or ZnL_n) were considered to have the potential to provide high regio- and stereoselectivity in the C−C bond forming step, together with lactone functional group tolerance. In the event, using the chromium(II) sources $CrCl_2$,[13] $CrCl_3/LiAlH_4$,[14] a catalytic chromium process ($CrCl_3$/Mn/TMSCl),[15] zinc with satd aq NH_4Cl in DMF,[16] or indium in the presence of a Lewis acid,[17] gave in all cases one major diastereoisomer of methylene lactone **5a** by crude ^1H NMR analysis (Table 1).

Table 1. Evalution of Different Allylation Conditions with **3** and Benzaldehyde



entry	conditions	yield of **5a** (%)	dr
1	$CrCl_2$ in DMF (rt, 15 h)	83	97:3
2	$CrCl_3/LiAlH_4$ in THF (rt, 15 h)	68	98:2
3	Cat. $CrCl_3$/Mn/TMSCl/*i*-Pr_2EtN in THF (rt, 15 h)	85	98:2
4	Zn/trace sat. aq NH_4Cl in DMF (rt, 15 h)	83	95:5
5	In/Eu$(OTf)_3$ in sat. aq NH_4Cl (rt, 15 h)	67	97:3

Due to the comparative experimental simplicity of the zinc protocol (Table 1 entry 4),[18] it was decided to evaluate the scope of the allylation process with different aromatic aldehydes under the zinc conditions (Table 2).

The chemistry was found to tolerate electron-rich (entries 4 and 6) and -deficient (entry 7) aromatic aldehydes and the presence of aryl halide (entries 2, 3 and 5), hydroxyl (entry 6), cyano (entry 7), and carbamate (entry 8) functionality. The stereochemistry of the major diastereoisomer **5b** arising from 1-naphthaldehyde (Table 2, entry 1) was established by X-ray crystallographic analysis[18] and is consistent with the transition state indicated in Scheme 1. Also, MOM protection of alcohol **5e** (Table 2, entry 4) gave a MOM ether[18] of established configuration, which has previously been converted into the insecticide

(3) (a) Lin, S.-H.; Chen, C.-C.; Vong, W.-J.; Liu, R.-S. *Organometallics* **1995**, *14*, 1619–1625. (b) Chen, C.-C.; Fan, J.-S.; Shieh, S.-J.; Lee, G.-H.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1996**, *118*, 9279–9287. (c) Shiu, L. H.; Wang, S.-L.; Wu, M.-J.; Liu, R. S. *J. Chem. Soc., Chem. Commun.* **1997**, 2055–2062. (d) Chandrasekharam, M.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 9122–9124.

(4) During the course of our studies, a single example of this process involving zinc with **3** and a complex chiral aldehyde was reported in a patent: (a) Xu, X.; Yang, H.; Qiao, X.; Xie, L. CN 101481367, 2009; *Chem. Abstr.*, 2009, *151*, 245843. (b) The reaction of zinc with **3** and formaldehyde has also been recently reported: Yang, H. S.; Qiao, X. X.; Cui, Q.; Xu, X. H. *Chin. Chem. Lett.* **2009**, *20*, 1023–1024.

(5) Abou El-Ela, M.; Jakupovic, J.; Bohlmann, F.; Ahmed, A. A.; Seif El-Din, A.; Khafagi, S.; Sabri, N.; El-Ghazouly, M. *Phytochemistry* **1990**, *29*, 2704–2706.

(6) Theodori, R.; Karioti, A.; Rancić, A.; Skaltsa, H. *J. Nat. Prod.* **2006**, *69*, 662–664. Corrigendum: *J. Nat. Prod.* **2009**, *72*, 804.

(7) The stereochemistries of **1** and **2** are currently not known with certainty.

(8) (a) Calderón, A.; de March, P.; el Arrad, M.; Font, J. *Tetrahedron* **1994**, *50*, 4201–4214. See also: (b) Chapleo, C. B.; Svanholt, K. L.; Martin, R.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 100–107.

(9) Murray, A. W.; Reid, R. *Synthesis* **1985**, 35–38.

(10) Ando, M.; Wada, T.; Isogai, K. *J. Org. Chem.* **1991**, *56*, 6235–6238.

(11) Hodgson, D. M.; Comina, P. J. In *Transition Metals for Fine Chemicals and Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 469−481.

(12) Luche, J. L.; Sarandeses, L. A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, 1999; pp 307−323.

(13) Nishitani, K.; Konomi, T.; Mimaki, Y.; Tsunoda, T.; Yamakawa, K. *Heterocycles* **1993**, *36*, 1957–1960.

(14) Okuda, Y.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481–484.

(15) Fürstner, A.; Shi, N. J. *Am. Chem. Soc.* **1996**, *118*, 12349–12357.

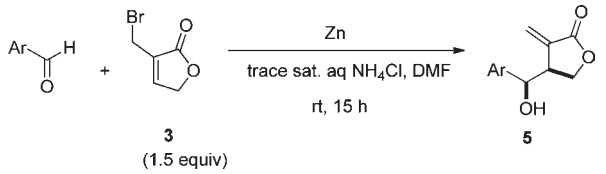
(16) Zinc in THF was very slow, giving only a trace of **5a** after 10 h. Zinc in DMF proceeded to completion, but required prolonged reaction time; the reaction was also accelerated by the addition of $PhCO_2H$ (1 equiv), albeit less efficiently than with NH_4Cl.

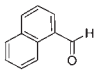
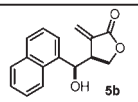
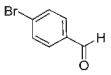
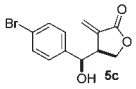
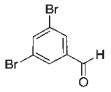
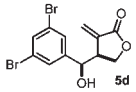
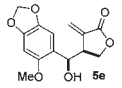
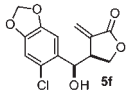
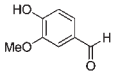
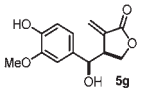
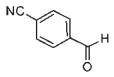
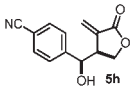
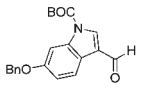
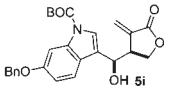
(17) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457–1460.

(18) See the Supporting Information for details.

(19) For details of aldehyde preparation see the Supporting Information.

Table 2. Scope of Allylation Using Bromolactone **3** with Zinc and Aromatic Aldehydes



entry	aldehyde	lactone **5**	yield of **5**	dr
1			79%	99:1
2			91%	94:6
3			78%	95:5
4[19]			73%	90:10
5			74%	90:10
6			71%	90:10
7			82%	90:10
8			67%	90:10

phrymarolin II.[20] The stereochemistry of vanillin-derived alcohol **5g** (Table 2, entry 6) was supported by subsequent 1,4-addition[21] of commercially available boronic ester **7**, which resulted in a concise, protecting group-free synthesis of the lignan hydroxymatairesinol (**8**)[22] (Scheme 3). The stereochemistry of **5a** and of the other alcohols in Table 2 was assigned by analogy.

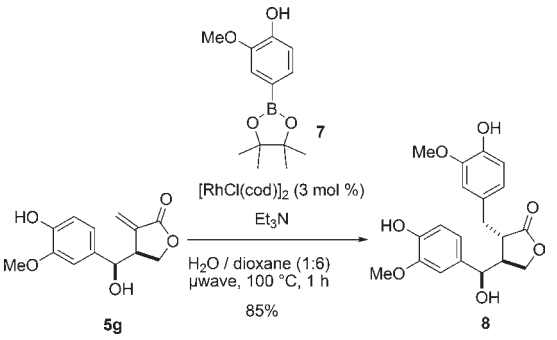
Reduction of diastereoselectivity was observed with nonaromatic aldehydes under the zinc allylation conditions: 83:17 dr (79% yield) with the aliphatic aldehyde docecanal and 55:45 dr (75% yield) with the α,β-unsaturated

(20) The spectral data were in full accord with the stereochemistry indicated in Table 2, entry 4, and also differed from the previously reported data for the diastereomeric MOM ether: (a) Yamauchi, S.; Yamamoto, N.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2209–2215. (b) Yamauchi, S.; Yamamoto, N.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1605–1613.

(21) (a) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821–1824. (b) de la Herrán, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csákÿ, A. G. *Org. Lett.* **2005**, *7*, 1669–1671.

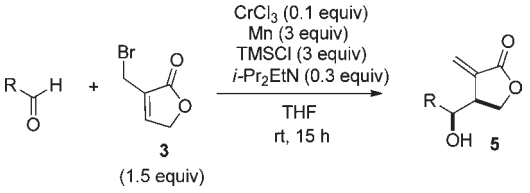
(22) (a) Freudenberg, K.; Knof, L. *Chem. Ber* **1957**, *90*, 2857–2869. (b) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345–1348.

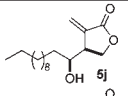
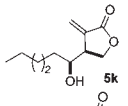
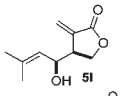
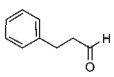
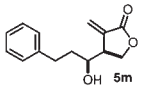
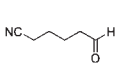
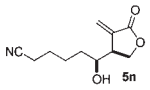
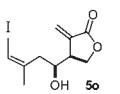
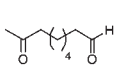
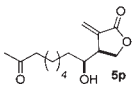
Scheme 3. Application of Allylation to (±)-Hydroxymatairesinol (**8**)



aldehyde 3-methylbut-2-enal. For such substrates we found that the cat. Cr(II) conditions (Table 1, entry 3) were more effective (Table 3). Excellent drs (98:2–99:1) were uniformly observed, aside from an α,β-unsaturated aldehyde (entry 3). The mild allylation conditions are indicated by the functional group tolerance of cyano, alkenyl iodide, and ketone functionality (entries 5–7) and the viability of a β,γ-unsaturated aldehyde (entry 6).

Table 3. Scope of the Allylation of Aliphatic Aldehydes Using Cat. Cr(II) conditions

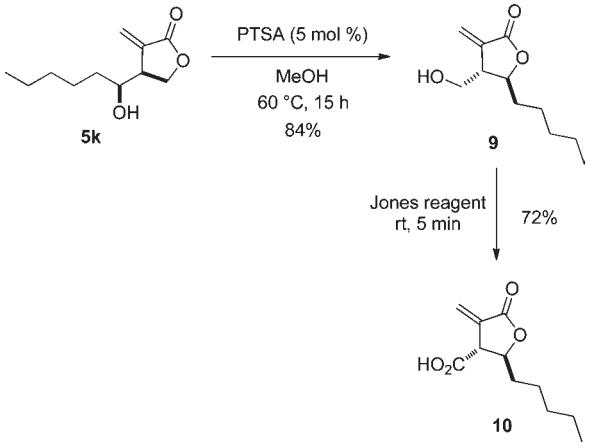


entry	aldehyde	lactone **5**	yield of **5**	dr
1			94%	99:1
2			93%	99:1
3			55%	88:12
4			75%	99:1
5[19]			65%	99:1
6[19]			56%	98:2
7[19]			70%	99:1

That the diastereoselectivity observed for aliphatic aldehydes is the same as found previously with the aromatic examples was supported by spectral comparison of methylene lactone **5j** (Table 3, entry 1) with the literature values[18,23] and by a further transformation of **5k** discussed below.

We also examined acid-catalyzed translactonization as a process to isomerize the β-hydroxymethylene products **5** generated in the above chemistry to *trans* β,γ-disubstituted α-methylenebutyrolactones (e.g., **9**, Scheme 4). The latter substitution pattern is found in many natural products (e.g., Figure 1).[1] Although the generation of primary alcohols from secondary alcohols by this approach has not been previously reported, it is known in a related *trans* β,γ-disubstitued α-methylenebutyrolactone that a less-hindered (Me-substituted) free secondary alcohol is favored (80:20−75:25) over a more hindered (*i*-Pr-substituted) free secondary alcohol at equilibrium.[3a,b] In the event, secondary alcohol **5k** (Table 3, entry 2) was recovered unchanged using the reported conditions (PTSA, CH_2Cl_2, rt, 15 h) for the secondary alcohol equilibration. However, reaction with 5% PTSA in MeOH (65 °C, 15 h) led smoothly to a 4:96 mixture in favor of the known[24] primary alcohol **9** (Scheme 4), which was cleanly isolated in 84% yield. The origin of the thermodynamic preference for primary alcohol **9**[25] may lie in reduction of destabilizing *gauche* interactions present in conformations of the secondary alcohol **5k**.[26] Jones oxidation[24] of primary alcohol **9** completed a short synthesis of the naturally occurring antibacterial and antitumor agent (±)-methylenolactocin (**10**).[3d,24]

Scheme 4. (±)-Methylenolactocin (**10**) by Translactonization



In summary, allylation of aldehyes using 3-(bromomethyl) furan-2(5*H*)-one (**3**) in the presence of zinc or Cr(II) salts provides a regio- and stereocontrolled access to β-substituted α-methylene-γ-butyrolactones. Conjugate addition and translactonization chemistry broaden the utility of the adducts, as illustrated in concise syntheses of (±)-hydroxymatairesinol (**9**) and (±)-methylenolactocin (**10**). Further applications in target synthesis and studies on asymmetric versions of this methodology are currently under investigation.

Acknowledgment. We thank Eli Lilly for funding (to E. P.A.T.) and B. Diseroad (Eli Lilly) for X-ray analysis.

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

Note Added after ASAP Publication. An error in Scheme 3 was corrected in the version reposted April 15, 2011.

(23) Hon, Y.-S.; Hsieh, C.-H.; Chen, H.-F. *Synth. Commun.* **2007**, *37*, 1635–1651. Allylation using the zinc conditions gave **5j** in 79% yield (83:17 dr). The minor diastereomer was determined to be that previously reported (see the Supporting Information).

(24) (a) Hon, Y.-S.; Hsieh, C.-H.; Liu, Y.-W. *Tetrahedron* **2005**, *61*, 2713–2723. (b) Saha, S.; Roy, S. C. *Tetrahedron* **2010**, *66*, 4278–4283.

(25) Submitting primary alcohol **9** to the reaction conditions gave the same 4:96 mixture of **5k**:**9** observed when starting with **5k**.

(26) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: Chichester, 1994; pp 682−684.