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A facile synthesis of chiral ω-allyl- and ω-*n*-propyllactones via asymmetric allylboration of formyl esters with *B*-allyldiisopinocampheylborane

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Abstract

Asymmetric allylboration of aldehydes containing an adjacent ester group with *B*-allyldiisopinocampheylborane, followed by hydrolysis and cyclization, provides the corresponding allyl substituted lactones in high yields and ≥92% enantiomeric excess. Hydrogenation of these lactones provides the corresponding propyl substituted lactones without any loss of optical purity.

Chiral lactones are important synthetic intermediates or end products in organic synthesis (Scheme 1). They can be olefinated via sequential phenylselenation, hydrogen peroxide oxidation, followed by selenoxide elimination.[2] Conversion of these olefinic lactones to hydroxy lactones as those present in mevilinic acid lactones are known.[3] Lactones can be functionalized at the α-position,[4] α-methylenized,[5] or converted to cyclic enol ethers.[6] Many of these lactones are biologically active.[4,7]

We considered several approaches to prepare chiral lactones using our asymmetric methods.[8] One of the standard methods for the preparation of chiral lactones is the asymmetric reduction of keto esters, followed by hydrolysis and cyclization.[9] Recently, we applied our inter- and intra-molecular asymmetric reduction with *B*-chlorodiisopinocampheylborane (DIP-Chloride™)[10] as a method to prepare aromatic lactones in high enantiomeric excess.[11] One of the applications of the optically active homoallylic alcohols derived via allylboration with *B*-allyldiisopinocampheylborane (**1**)[12] has been the synthesis of γ-butyrolactones via a protection–hydroboration–oxidation–deprotection–cyclization sequence (Eq. 1).[13] Although this procedure provides a variety of γ-substituted γ-butyrolactones, it is limited to the synthesis of five-membered lactones.

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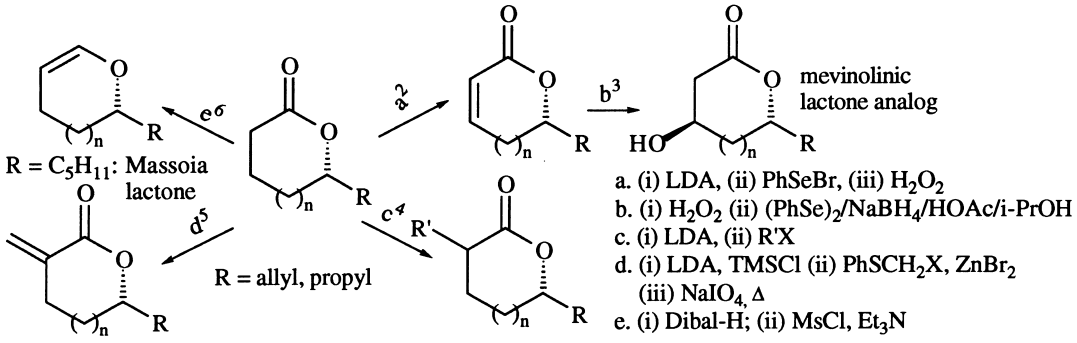
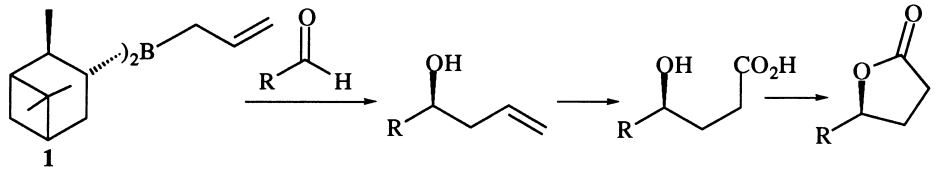
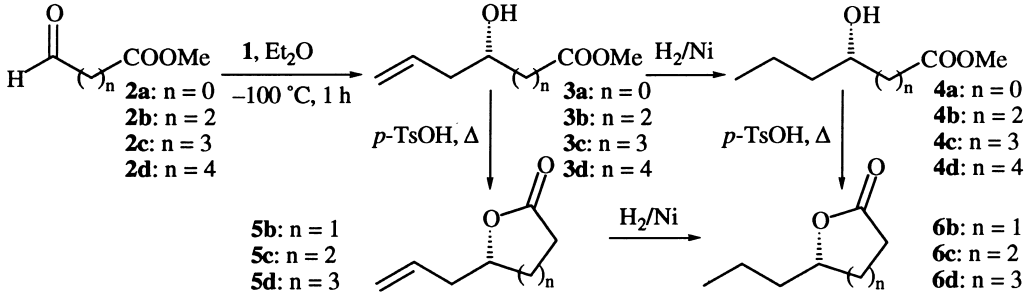


Scheme 1.



(1)

We discerned that allylboration of aldehydes possessing an appropriate ester moiety should provide the corresponding homoallylic alcohol, which upon hydrolysis and cyclization should furnish the respective lactones (Scheme 2). This strategy was effectively applied for the synthesis of 5-, 6-, and 7-membered lactones in very high enantiomeric excess (ee). The propyl substituted lactones were synthesized by hydrogenating either the unsaturated lactones or homoallylic alcohols prior to cyclization. Our results are presented later.



Scheme 2.

Initially we carried out the allylboration of methyl glyoxylate (**2a**)[14] with **1** in ethyl ether at −100°C. The reaction was complete within 1 h. The usual work-up provided the corresponding homoallylic alcohol ester **3a** in 82% yield. Analysis of the product using the CHIRACEL® OD-H™ column[15] for HPLC revealed an ee of 94%. Hydrogenation of **3a** provided methyl 2-hydroxypentanoate (**4a**). We encountered no difficulty in extending the reaction to methyl 4-oxobutanoate (**2b**),[16] methyl 5-oxopentanoate (**2c**),[16] and methyl 6-oxohexanoate (**2d**).[17] The corresponding homoallylic alcohol esters **3b–d** were obtained in 82%, 88%, and 80% yields and ≥99%, 96%, and 92% ee, respectively. The ee of **3b** was determined on a β-DEX-120™ capillary column[18] using a gas chromotograph. The ee of **3c** was determined using HPLC, as in the case of **3a**, and confirmed by ^{1}H NMR analysis of its acetate using $Eu(hfc)_3$ as the shift reagent. The ee of **3d** was determined by ^{1}H NMR spectroscopy of the corresponding acetate in the presence of $Eu(hfc)_3$. Hydroxy ester **3b** was partially (~50%) lactonized during the work-up. Complete lactonization was achieved by treating it with *p*-TsOH. Ester **3c** was lactonized in the presence of *p*-TsOH in refluxing toluene within 5 h. Attempts to lactonize **3d** to **5d**

Table 1
Allylboration of formyl esters with *B*-allyldiisopinocampheylborane

formyl ester	homoallylic alcohol ester: product	isol. yield, %	% ee	conf.	$[\alpha]_D^{20}(CHCl_3)$
methyl glyoxylate (**2a**)	**3a**	82	94[a]	*S*[b]	+16.13 (*c* 2.24)
methyl 4-oxo-butanoate (**2b**)	**3b**	82[c]	≥ 99[d]	*R*[e]	+12.76 (*c* 2.7)
methy 5-oxo-pentanoate (**2c**)	**3c**	88	96[a,f]	*R*[e]	+ 4.55 (*c* 1.67)
methyl 6-oxo-hexanoate (**2d**)	**3d**	80	92[f]	*R*[e]	+ 7.43 (*c* 1.62)

[a]Ee determined by HPLC. [b]Configuration determined by comparing the rotation of the hydrogenated product. [c]Combined yield of lactone and hydroxy ester. [d]Ee determined by GC. [e]Configuration determined by conversion to the propyllactones and comparing the rotation. [f]Ee determined by ^1H NMR.

Table 2
Hydrogenation of homoallylic esters[20]

homoallylic ester	propyl alcohol ester: product #	yield, %	% ee	conf.	$[\alpha]_D^{20}$ ($CHCl_3$)
3a	**4a**	94	94	*S*[a]	+11.38 (*c* 1.52)[a]
3b	**4b**	96	≥ 99[b]	*S*[b]	+ 4.94 (*c* 1.56)
3c	**4c**	95	96[b]	*S*[b]	+ 1.29 (*c* 1.25)
3d	**4d**	92	92[b]	*S*[b]	+ 1.34 (*c* 1.57)

[a]Lit.[20] $[\alpha]_D^{20}$ = +9.84 (*c* 1.26, $CHCl_3$) for 88% ee (*S*). [b]Ee and configurations determined by comparing the rotations of the propyllactones.

Table 3
Synthesis of allyl and propyl lactones[21]

allyl lactone	isol. yield, %	ee[a] %	conf.[a]	$[\alpha]_D^{20}$ ($CHCl_3$)	propyl lactone	isol. yield, %	ee %	conf.	$[\alpha]_D^{20}$
5b	90	≥ 99	*R*	-17.22 (*c* 2.1)	**6b**	93	≥ 99	*S*	-55.7 (*c* 1.82)[c]
5c	94	96	*R*	-32.4 (*c* 1.73)	**6c**	90	96	*S*	-60.9 (*c* 0.98)[d]
5d	70[b]	92	*R*	-40.56 (*c* 1.22)	**6d**	95	92	*S*	-38.3 (*c* 1.32)[e]

[a]Ee and configurations determined by comparing the rotations of the propyllactones. [b]Lactonization of hydroxy acid achieved with 1-methyl-2-chloro-pyridinium iodide.[19] [c]Lit.[9] $[\alpha]_D^{20}$ = +56.2 (*c* 1.56, THF) for ≥ 98% ee (*R*). [d]Lit.[9] $[\alpha]_D^{20}$ =+63.9 (*c* 1.37, THF) for ≥ 98% ee (*R*). [e]Lit.[21] $[\alpha]_D^{20}$ = -32.0 (*c* 1.4, $CHCl_3$) for 97% ee.

under similar conditions gave a complex mixture of products. However, **5d** was prepared in 45% yield via hydrolysis of **3d** to the corresponding hydroxy acid, followed by lactonization. An improved yield (70%) of **5d** was achieved by cyclizing the hydroxy acid in the presence of 1-methyl-2-chloropyridinium iodide.[19] The enantiomeric purity and configurations of all of the lactones determined by comparison with literature values showed no loss of optical activity during lactonization. Hydrogenation of these lactones using H_2 over Raney Ni in ethyl acetate provided the corresponding *n*-propyl lactones. These saturated lactones were also synthesized by hydrogenation of the homoallylic alcoholic esters, followed by lactonization. The results are summarized in Tables 1–3.

In conclusion, we have carried out the asymmetric allylboration of aldehydes containing an adjacent ester group in high ee with *B*-allyldiisopinocampheylborane. The product hydroxy esters upon cyclization provided the corresponding ω-allyl substituted 5-, 6-, and 7-membered lactones in high yields and ee. Hydrogenation of these lactones to the corresponding *n*-propyl substituted lactones was also achieved without any loss of optical purity. Typical experimental procedures are as follows.

*Allylboration of **2c***: All operations were carried out under a nitrogen atmosphere. To a stirred solution

of (−)-*B*-allyldiisopinocampheylborane[12] was added, at −100°C, methyl 5-oxopentanoate (**2c**) (1.3 g, 10 mmol) in 5 ml of Et_2O. The mixture was stirred at this temperature for 1 h, 1 ml of methanol was added, warmed to rt, oxidized with 3 M NaOH (4 ml) and 30% H_2O_2 (5 ml), and stirred for 4 h. The product was extracted with Et_2O, washed with brine, and dried over anhydrous $MgSO_4$. Removal of the solvent provided a crude product which was separated from isopinocampheol by silica gel column chromatography (hexane:ethyl acetate, 9:1) to obtain 1.52 g of methyl 5-hydroxy-7-octenoate (**3c**) as a liquid. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.47 (m, 2H), 1.75 (m, 3H), 2.14 (m, 1H), 2.32 (m, 3H), 3.65 (m, 4H), 5.13 (m, 2H), 5.81 (m, 1H); ^{13}C NMR δ ($CDCl_3$) (ppm): 21.04, 33.85, 36.06, 41.96, 51.54, 70.17, 118.18, 134.67, 174.14.

*Hydrogenation of **3c***: Raney Ni (50 mg of 50% slurry in water) taken in a 25 ml flask was washed with methanol (2×3 ml). Ethyl acetate (5 ml) was added to the flask, followed by **3c** (0.172 g, 1 mmol) dissolved in 1 ml EtOAc. The flask was purged with hydrogen and closed under a positive pressure of hydrogen. The reaction was monitored by the consumption of hydrogen using a gasimeter. Upon completion (~2 h), the reaction mixture was filtered, the solvent removed, and purified by silica gel column chromatography to afford methyl 5-hydroxyoctanoate (**4c**) as a liquid. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 0.92 (t, *J*=7.1 Hz, 3H), 1.45 (m, 6H), 1.74 (m, 3H), 2.35 (t, *J*=7.0 Hz, 2H), 3.61 (m, 1H), 3.69 (s, 3H); ^{13}C NMR δ ($CDCl_3$) (ppm): 14.09, 18.82, 21.01, 33.92, 36.74, 39.67, 51.54, 71.09, 174.25.

*Lactonization of **3c***: Methyl 5-hydroxy-7-octenoate (**3c**) (0.172 g, 1 mmol) was dissolved in 10 ml of toluene contained in a 25 ml flask fitted with a Dean–Stark trap. *p*-TsOH (17 mg, 10 mol%) was then added and refluxed for 5 h. Toluene was evaporated and the crude product was purified by silica gel column chromatography to provide 0.133 g (95%) of (6*R*)-allyltetrahydropyranone (**5c**) as a liquid. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 1.56 (m, 1H), 1.88 (m, 3H), 2.49 (m, 4H), 4.35 (m, 1H), 5.15 (m, 2H), 5.82 (m, 1H); ^{13}C NMR δ ($CDCl_3$) (ppm): 18.46, 27.22, 29.48, 40.06, 79.80, 118.55, 132.65, 171.62.

*Hydrogenation of **5c***: Hydrogenation was carried in a similar way to that described for **3c**. (6*R*)-*n*-Propyltetrahydropyranone **6c** was isolated as a liquid in 90% yield. ^{1}H NMR (300 MHz) δ ($CDCl_3$) (ppm): 0.95 (t, *J*=7.4 Hz, 3H), 1.48 (m, 4H), 1.70 (m, 1H), 1.84 (m, 3H), 2.43 (m, 1H), 2.58 (m, 1H), 4.30 (m, 1H); ^{13}C NMR δ ($CDCl_3$) (ppm): 13.86, 18.21, 18.53, 27.83, 29.49, 37.93, 80.35, 171.99.

*Lactonization of **4c***: The lactonization was achieved as described earlier to provide **6c** in 96% yield.

Acknowledgements

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