Pergamon

Tetrahedron Letters 41 (2000) 583–586

TETRAHEDRON LETTERS

Asymmetric synthesis of goniothalamin, hexadecanolide, massoia lactone, and parasorbic acid via sequential allylboration–esterification ring-closing metathesis reactions

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Received 16 September 1999; revised 9 November 1999; accepted 12 November 1999

Abstract

Acrylic esters of homoallylic alcohols prepared in 92–97% ee via the asymmetric allylboration of appropriate aldehydes with *B*-allyldiisopinocampheylborane, when refluxed in dichloromethane in the presence of 10 mol% of Grubbs' catalyst provided the natural enantiomers of (*S*)-(+)-parasorbic acid, (*R*)-(–)-massoia lactone, and (*R*)-(+)-goniothalamin. (*S*)-(–)-Hexadecanolide was prepared by hydrogenating the corresponding lactenone synthesized using the above sequence.

Keywords: asymmetric synthesis; allylboration; metathesis.

Chiral lactenones and lactones are functionalities commonly present in a number of natural products that function as pheromones or medicinal compounds. They often act as intermediates for the synthesis of other natural products. For example, (*S*)-(+)-5,6-dihydro-6-methyl-2*H*-pyran-2-one (parasorbic acid, **1a**), a natural product isolated from mountain ash berries (*Sorbus aucuparia*), is an intermediate for the synthesis of several carbohydrate derived antibiotics.[1] This intermediate has been converted into *cis*-3,6-dimethyltetrahydropyran-2-one, the major component of the male carpenter bee pheromone.[2] Similarly, (*R*)-(–)-5,6-dihydro-6-pentyl-2*H*-pyran-2-one (massoia lactone, **1b**), isolated from bark oil of *Criptocarya massoia*[3a] and jasmine flowers[3b] is also found in the defense secretion of two species of formicin ants of the genus *Camponotus*.[3c] (6*R*, 2′*E*)-(+)-6-(2′-Phenylvinyl)-5,6-dihydro-2*H*-pyran-2-one (goniothalamin, **1c**), a natural product with excellent medicinal properties has been isolated from several sources.[4] This is a key intermediate for the synthesis of several mevinolic acid analogs.[5] (*S*)-(–)-6-Undecyltetrahydropyran-2-one (hexadecanolide, **2d**), isolated from[6] the mandibular glands of the oriental hornet *Vespa orientalis*, also contains a δ-valerolactone moiety.

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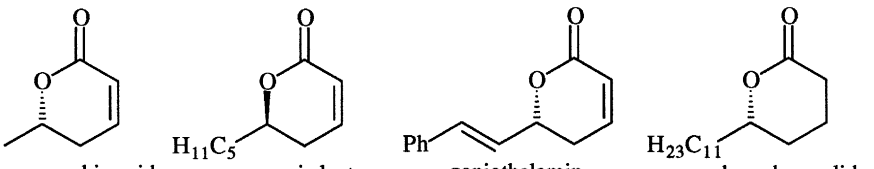
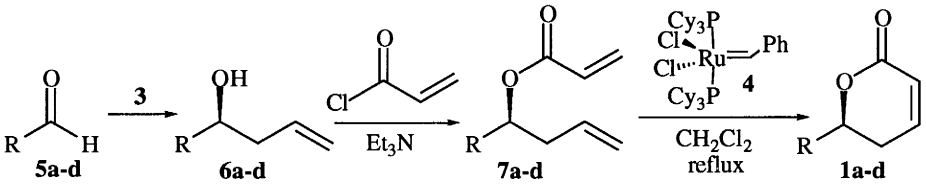
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02130-9



Several approaches to prepare these important chiral lactenones and lactones have been made in the literature, often involving multi-step sequences with or without resolution of racemic mixtures.[7–11]

For the past two decades, we have been developing several chiral organoborane reagents for asymmetric transformations.[12] During these projects, we have demonstrated the utility of our reagents for the synthesis of optically active lactones.[13] For example, we applied our inter- and intra-molecular asymmetric reduction with *B*-chlorodiisopinocampheylborane (DIP-Chloride™)[14] for the preparation of aromatic lactones in high enantiomeric excess (ee).[13a] One of the applications of the optically active homoallylic alcohols derived via allylboration with *B*-allyldiisopinocampheylborane (**3**)[15] has been the synthesis of γ-butyrolactones via a protection–hydroboration–oxidation–deprotection–cyclization sequence.[13b] Also, we carried out the allylboration of aldehydes possessing an appropriate ester moiety, followed by hydrolysis and cyclization to prepare ω-allyl and ω-*n*-propyl substituted five- to eight-membered lactones in very high ee.[13c]

During the past few years, ring-closing metathesis reactions have been developed as an efficient route to achieve the synthesis of lactenones and lactones of different ring sizes.[16] Of the several catalysts developed for this purpose, Grubbs' bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (**4**) has received considerable attention.[17] We envisaged a general chiral synthesis of 6-substituted-5,6-dihydro-2*H*-pyran-2-ones via an asymmetric allylboration–esterification–cyclization strategy (Scheme 1). Our successful synthesis of **1a**–**d** using this strategy is described herein.



Scheme 1.

Allylboration of acetaldehyde (**5a**) with (+)-*B*-allyldiisopinocampheylborane ((+)-**3**) in an Et_2O-pentane mixture at –100°C provided (*S*)-(+)-4-penten-2-ol (**6a**) in 94% ee.[15] Esterification of **6a** with acryloyl chloride provided an 80% yield of the corresponding acryloyl ester **7a**, which when treated with 10% of **4** in refluxing CH_2Cl_2 for 6 h provided **1a** in 81% yield. Similar reaction sequence with hexanal (**5b**),[18] cinnamaldehyde (**5c**), and *n*-dodecanal (**5d**) provided **1b**, **1c**, and **1d** in 97%, 92%, and 92% ee, respectively. Hydrogenation of **1d** in the presence of Pd/C provided a quantitative yield of **2d**. In all of the ring-closing metathesis reactions, we obtained identical results in the presence or absence of a catalytic amount of Ti(*i*-PrO)$_4$.[16,19]

All of the results are summarized in Table 1.

In conclusion, we have carried out the synthesis of a series of naturally occurring 6-substituted-5,6-dihydro-2*H*-pyran-2-ones in high ees via a sequential asymmetric allylboration–esterification ring-closing metathesis sequence. The 6-undecyl derivative was hydrogenated to the naturally occurring hexadecanolide. We believe that this three-step reaction sequence is considerably simpler compared to the

Table 1
Preparation of lactenones via allylboration–esterification ring-closing metathesis

aldehyde	homoallylic alcohol #	yield, %	lactenone #	yield, %	% ee[a]	conf.	$[\alpha]_D^{20}$
acetaldehyde (**5a**)	**6a**	70	**1a**	81	94	*S*	+193.2 (*c* 1.6, EtOH)[b]
n-hexanal (**5b**)	**6b**	71	**1b**	84	97	*R*	–113.6 (*c* 1.36, $CHCl_3$)[c]
cinnamaldehyde (**5c**)	**6c**	72	**1c**	76	92	*R*	+160.2 (*c* 0.8, $CHCl_3$)[d]
n-dodecanal (**5d**)	**6d**	74	**1d**	86	92	*S*	+77.2 (*c* 1.3, THF)[e]

[a]Determined by HPLC analysis on a CHIRALCEL® OD-H™ of the intermediates. [b]$[\alpha]_D^{25}$ = +198 (*c* 0.6, EtOH) for 98% ee (*S*).[7a] [c]$[\alpha]_D^{29}$ = –107.5 (*c* 1.07, $CHCl_3$) for ≥ 98% ee (*R*).[8a] [d]$[\alpha]_D^{20}$ = +170.3 (*c* 1.38, $CHCl_3$) for 100% ee (*R*).[4a] [e]$[\alpha]_D^{20}$ = +78.7 (*c* 1.0, THF) for 100% ee (*S*).[10a]

several procedures described in the literature for the synthesis of these types of lactenones and lactones. This procedure can be extended to the synthesis of several other natural products.[20]

The experimental procedure for the synthesis of massoia lactone is representative.

Allylboration of **5b**: All operations were carried out under a nitrogen atmosphere. To a stirred solution of (–)-*B*-allyldiisopinocampheylborane (prepared from DIP-Chloride™)[21] was added, at –100°C, hexanal (**5b**) (1.0 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, and worked up as usual with NaOH and H_2O_2. 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, 95:5) to obtain 1.01 g (71%) of (*R*)-(+)-1-nonen-4-ol (**6b**) as a liquid. This was dissolved in 10 mL of CH_2Cl_2, cooled to 0°C, and 0.86 mL (10.5 mmol) of acryloyl chloride and 2.92 mL (21 mmol) of Et_3N were added, warmed to rt and stirred for 4 h. The resulting mixture was filtered through a short pad of Celite to remove solid $Et_3N{\cdot}HCl$, poured into water and the product was extracted with CH_2Cl_2. The crude product was purified by silica gel column chromatography (hexane:ethyl acetate, 99:1) and concentrated to obtain 1.14 g (82%) of **7b**.

Grubbs' catalyst (0.16 g, 0.02 mmol, 10 mol%) was dissolved in 5 mL of CH_2Cl_2 and was added dropwise to a refluxing solution of the above acrylic ester (0.39 g, 2 mmol) in 200 mL of CH_2Cl_2. Refluxing was continued for 6 h by which time all of the starting material was consumed (TLC). The solvent was removed under aspirator vacuum and the crude product was purified by silica gel column chromatography (hexane:ethylacetate, 75:25) to obtain 0.28 g (84%) of **1b**. The spectral data matched those reported.

Acknowledgements

Financial assistance from the Purdue Borane Research Fund is acknowledged.

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