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Total syntheses of (*R*)-argentilactone and (*R*)-goniothalamin via catalytic enantioselective allylation of aldehydes

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Abstract—The total syntheses of (*R*)-argentilactone (five steps, 25% overall yield) and (*R*)-goniothalamin (three steps, 61% overall yield) have been described through the enantioselective catalytic allylation of aldehydes (including a propargylic aldehyde) which provided a rapid access to these natural products that display very interesting biological activities.

In 1977, Rúveda and co-workers reported the isolation of argentilactone (**1**) from *Aristolochia argentina* (*Aristolochiaceae*) (Fig. 1).[1] This compound was also isolated from *Chorisia crispflora* (*Bombaceae*)[2] and *Annona haematantha* (*Annonaceae*).[3] Later, this natural pyranone was shown to have antileishmanial activity equivalent to the reference drug *N*-methylglucamine antimonate against *Leishmania amazonensis*,[3] as well as cytotoxic activity against mouse leukaemia cells (P-388).[2]

Goniothalamin (**2**) was isolated in 1967 from the dried bark of *Cryptocarya caloneura* (Fig. 1).[4] Later it was isolated from *Cryptocarya moschata*,[5] *Bryonopsis laciniosa*[6] and various species of *Goniothalamus*.[7] It is a potential cytotoxic compound that has been demonstrated to have antiproliferative activities in a number of transformed cell lines including MCF-7 (breast carcinoma) and HeLa cells (human cervical carcinoma).[8,9] Recent studies have indicated that goniothalamin induces apoptosis in JurKat T-cells through activation of two members of the cysteine proteases family, caspases-3 and 7.[10] Deregulation of apoptosis has now been implicated in the onset or progression of cancer.[11] Consequently, apoptosis represents an innate cellular defense against carcinogen-induced cellular damage by removing and inhibiting survival and growth of altered cells at different stages of carcinogenesis.

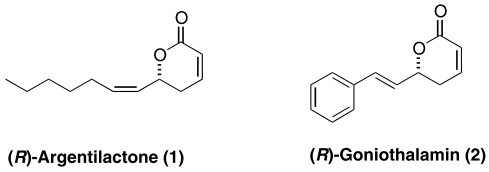

Figure 1. Structures of (*R*)-argentilactone (**1**) and (*R*)-goniothalamin (**2**).

Both argentilactone (**1**) and goniothalamin (**2**) contain the 5,6-dihydro-2*H*-pyran-2-one moiety and bear the (*R*)-configuration in their natural form. This important structural motif also occurs in other highly active substances, e.g. kurzilactone (cytotoxic),[12] leptomycin B (antifungal),[13] ratjadone (cytotoxic),[14] and strictifolione (antifungal).[15] Due to the interesting biological activity displayed by argentilactone (**1**) and goniothalamin (**2**), several successful approaches to these natural products have been reported.[16,17] The absolute configuration in the pyran-2-one moiety has generally been secured from chiral starting material or through asymmetric reduction using enzymes or microorganisms.[16,17] A noteworthy exception is the asymmetric allylboration of aldehydes with *B*-allyldiisopinocampheylborane developed by Brown and co-workers.[18] While high levels of enantiomeric excess and yield are generally achieved, the use of a stoichiometric amount of the chiral allylborane is not the more efficient solution for the transfer of chirality and catalytic asymmetric protocols are certainly a more attractive alternative to chiral non-racemic 6-substituted 5,6-dihydro-2*H*-pyran-2-ones.[19]

As one of the fundamental and powerful C–C bond-forming reactions, catalytic enantioselective allylation of aldehydes attracted considerable attention in asymmetric synthesis.[20] Particularly, Maruoka and co-workers have developed a new class of highly reactive and

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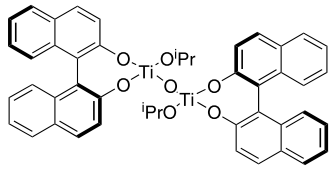


(*S*,*S*)-**A**

Figure 2. The μ-oxo bis(binaphthoxy)(isopropoxy)titanium complexes (*S*,*S*)-**A** developed by Maruoka and co-workers.

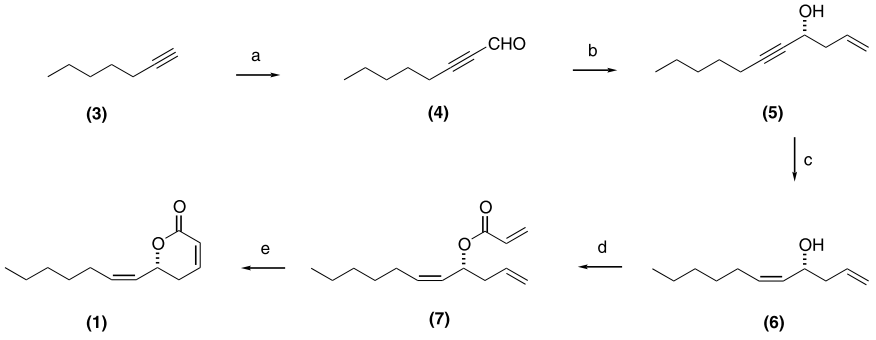
selective titanium complexes for the allylation of aldehydes.[21,22] The μ-oxo bis(binaphthoxy)(isopropoxy)-titanium complex (*S*,*S*)-**A** (Fig. 2), which display excellent enantioselectivity for the addition of allyltributyltin to aldehydes, including cinnamaldehyde.[22] The efficiency of this catalyst is proposed to be due to simultaneous coordination and double activation ability of the bidentate Ti(IV) catalyst (*S*,*S*)-**A**.

In this work, we describe the total synthesis of argentilactone (**1**) and goniothamin (**2**) from 1-heptyne and *trans*-cinnamaldehyde respectively, featuring enantioselective Maruoka allylation[22] and ring-closing metathesis as the key steps.

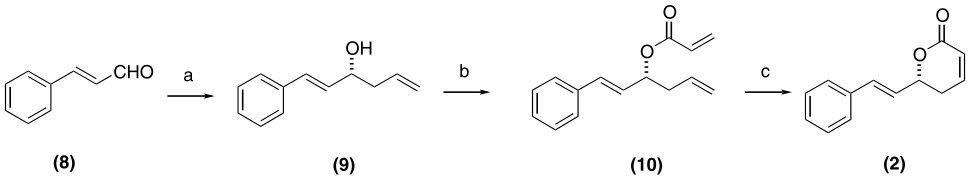
Our approach to argentilactone (**1**) centered around the catalytic asymmetric allylation of propargylic aldehyde **4**, prepared in 65% yield from 1-heptyne (treatment with *n*-BuLi, followed by reaction with DMF). Despite the recent developments in the catalytic asymmetric allylation catalyzed by chiral Lewis acids, no successful example with propargylic aldehydes has yet been reported.[20] In the event, the enantioselective addition of allyltributyltin propargylic aldehyde **4** under the influence of in situ generated chiral (*R*,*R*)-**A** complex (CH_2Cl_2, −20°C for 24 h), afforded **5** in 89% yield and 86% ee. Enantiomeric excess was determined by chiral GC (column Chirasil-DEX CB) after conversion of propargylic alcohol **5** to (*Z*)-allylic alcohol **6** [Lindlar catalyst, quinoline, EtOAc:1-octene (1:1, v/v), H_2 (1 atm), 30 min, rt] in 74% yield.[23] Ring-closing metathesis[24] of **7**, prepared in 86% yield from homoallylic alcohol **6** and acryloyl chloride, with 10 mol% of Grubbs' catalyst in refluxing CH_2Cl_2 for 6 h (70% yield) provided argentilactone (**1**)[25] in 25% overall yield from **3** (Scheme 1).

The above methodology proved also to be of value in the total syntheses of goniothalamin (**2**). Catalytic asymmetric allylation of *trans*-cinnamaldehyde (**8**) with allyltributyltin, under the influence of chiral (*R*,*R*)-**A** complex (CH_2Cl_2, −20°C, 24 h) afforded **9** in 78% yield and 96% ee. Enantiomeric excess was determined by chiral GC (column Chirasil-DEX CB) after conversion of allylic alcohol **9** to acrylate **10** (acryloyl chloride, Et_3N, cat. DMAP in CH_2Cl_2 at −23°C) in 80% yield. When compared to other catalytic asymmetric allylation protocols, the one developed by Maruoka and co-workers provided higher level of enantioselection in the addition of allyltributyltin to *trans*-cinnamaldehyde.

Ring-closing metathesis[24] of **10** with 10 mol% Grubbs' catalyst in refluxing CH_2Cl_2 for 12 h (98% yield) furnished goniothalamin (**2**)[26] in 61% overall yield from cinnamaldehyde (Scheme 2).



Scheme 1. Total synthesis of (*R*)-argentilactone (**1**). *Reagents and conditions*: (a) *n*-BuLi (1.5 M in hexane, 1.2 equiv.), Me_2NCHO (2.0 equiv.), THF −78 to 0°C (65%); (b) (*R*)-BINOL (10 mol%), $Ti(OiPr)_4$ (15 mol%), $TiCl_4$ (5 mol%), Ag_2O (10 mol%), allyltributyltin (1.1. equiv.), CH_2Cl_2, −20°C, 24 h (89%; 86% ee); (c) Lindlar catalyst (10 mol%), quinoline (2.0 equiv.), EtOAc:1-octene (1:1) (74%); (d) acryloyl chloride (1.8 equiv.), Et_3N (3.6 equiv.), CH_2Cl_2, 0°C (86%); (e) Grubbs' catalyst [$(Pcy_3)_2Cl_2Ru$=CHPh] (10 mol%), CH_2Cl_2 (70%).



Scheme 2. Total synthesis of (*R*)-goniothalamin (**2**). *Reagents and conditions*: (a) (*R*)-BINOL (10 mol%), $Ti(OiPr)_4$ (15 mol%), $TiCl_4$ (5 mol%), Ag_2O (10 mol%), allyltributyltin (1.1. equiv.), CH_2Cl_2, −20°C, 24 h (78%; 96% ee); (b) acryloyl chloride (1.8 equiv.), Et_3N (3.6 equiv.), CH_2Cl_2, 0°C (80%); (c) Grubbs' catalyst [$(Pcy_3)_2Cl_2Ru$=CHPh] (10 mol%), CH_2Cl_2 (98%).

In this work, we carried out the total syntheses of (*R*)-argentilactone (**1**) in five steps and 25% yield from 1-heptyne and (*R*)-goniothalamin (**2**) in three steps and 61% overall yield from *trans*-cinnamaldehyde. This concise and efficient approach compares favorably with the more efficient approaches so far reported in the literature for these natural products[16a,17a] and illustrates the utility of the asymmetric catalytic allylation protocol developed by Maruoka and co-workers to provide rapid access to chiral 6-substituted pyran-2-ones. The extension of the methodology described herein to synthesis of other natural pyranones is underway in our laboratory.

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25. **Representative analytical data for (*R*)-argentilactone**: IR (film): 3020, 2956, 2927, 2858, 1722, 1466, 1381, 1244, 1149, 1055, 1022, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (ddd, 1H, $J=9.7$, 5.5, 3.1 Hz), 6.05 (ddd, 1H, $J=9.7$, 2.2 and 1.4 Hz), 5.71–5.52 (m, 2H), 5.22 (ddd, 1H, $J=10.2$, 8.4 and 4.9 Hz), 2.49–2.30 (m, 2H), 2.17–2.03 (m, 2H), 1.46–1.26 (m, 6H), 0.90 (t, 3H, $J=7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 144.6, 135.5, 126.3, 121.5, 73.9, 31.5, 29.9, 29.1, 27.8, 22.5, 14.1. $[\alpha]_D=-22$ (*c* 2.2, EtOH), {lit.,[4] $[\alpha]_D=-21.1$ (*c* 2.3, EtOH)}.

26. **Representative analytical data for (*R*)-goniothalamin**: mp 81–82°C, {lit.,[7c] mp 85°C}; IR (film): 3055, 3024, 2924, 1720, 1246, 814, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.25 (m, 5H), 6.92 (dt, 1H, $J=9.5$ and 4.0 Hz), 6.72 (d, 1H, $J=15.9$ Hz), 6.27 (dd, 1H, $J=15.9$ and 6.2 Hz), 6.08 (d, 1H, $J=9.5$ Hz), 5.10 (q, 1H, $J=6.9$ Hz), 2.56–2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 144.5, 135.5, 132.8, 128.5, 128.1, 126.5, 125.5, 121.4, 77.8, 29.8. $[\alpha]_D=+164$ (*c* 1.7, $CHCl_3$), {lit.,[7c] $[\alpha]_D=+170.3$ (*c* 1.38, $CHCl_3$)}.