A Short and General Approach to the Synthesis of Styryllactones: (+)-Goniodiol, its Acetates and β-Trifluoromethyl Derivative, (+)-7-*epi*-Goniodiol and (+)-9-Deoxygoniopypyrone

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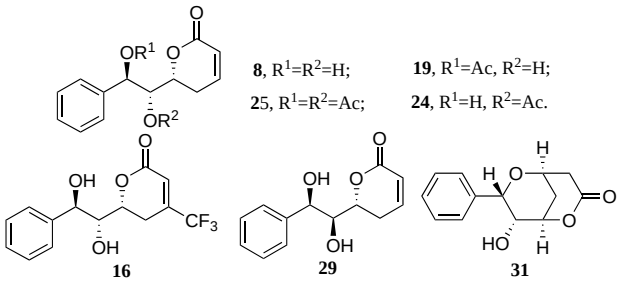
Abstract: (+)-Goniodiol, its acetates and β-trifluoromethyl derivative, (+)-7-*epi*-Goniodiol and (+)-9-deoxygoniopypyrone, the representatives of styryllactones have been synthesized in a short and general way. The key steps involve the regioselective asymmetric dihydroxylation and the palladium-catalyzed cross-coupling of cyclic allylic carbonate with vinyltributylstannane.

Key words: (+)-Goniodiol, styryllactones, synthesis, asymmetric dihydroxylation, cross-coupling

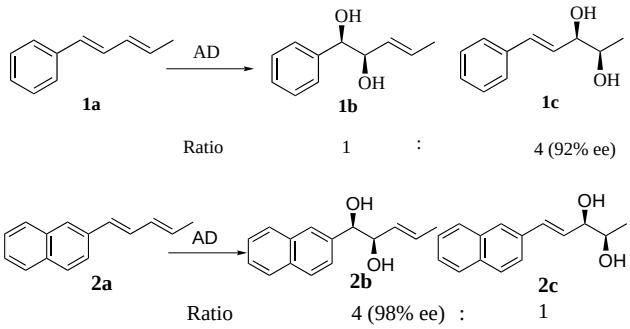
The Asian trees of the genus Goniothalamus have long been recognized as a source of chemotherapeutic agents. The extracts from leaves of Goniothalamus have traditionally been used for the treatment of edema and rheumatism,[1a] as well as a pain killer and arbortifacient.[1b,c] Recent publications by McLaughlin[2] have disclosed the isolation and characterization of a number of novel so-called styryllactones from Goniothalamus giganteus, which were found to be marginally to significantly cytotoxic against various human tumors. Because of their unique structural features and potent biological activities, much efforts have been centered on the development of methodology for the synthesis of these styryllactones.[3] Most of the synthetic strategies in the literatures are starting from chiral materials, such as sugars, tartaric acid, mandelic acid and 2,3-*O*-isopropylidene-D-glyceraldehyde.[4] Herein, we describe a short and general route to asymmetric synthesis of the representatives of styryllactones, such as (+)-Goniodiols (**8**, **19**, **16**, **24**, **25**), (+)-7-*epi*-goniodiol (**29**) and (+)-9-deoxygoniopypy-rone (**31**) (Figure), where the key steps involve the regioselective asymmetric dihydroxylation and the palladium-catalyzed cross-coupling of cyclic allylic carbonate with vinyltrimethylstananne.

Our synthesis began with the enantioselective dihydroxylation of (*E*)-1-phenyl-1, 3-butadiene **3a**. Olefins with conjugated aromatic substituents are of particular interest as substrates for the asymmetric dihydroxylation since the products obtained are always encountered with high ees together with unpredictable regioselectivities.[5a–c] Sharpless reported[5a] that regioselectivities of the asymmetric dihydroxylation of these conjugated aromatic dienes, such as compound **1a**, showed a slightly greater preference for



Figure

the double bond distal to the aromatic ring (Scheme 1). This preference for attacking the outer double bond is not surprising given that oxidation occurred at the internal site leading to greater disruption of conjugation. In contrast, in the case of β-naphthyl substituted diene **2a** the internal double bond is oxidized predominantly, implying that the 'disruption of conjugation' effect has somehow been overcome. They attributed this preference for dihydroxylation of the internal double bond to favorable stacking interactions between the naphthyl group and the binding pocket of the phthalazine ligand.



Scheme 1 Asymmetric dihydroxylation of conjugated dienes using $(DHQD)_2$-PHAL as ligand at 0 °C.

We therefore were interested in exploration of the situation of asymmetric dihydroxylation taken place on the terminal conjugated double bonds such as the substrate (*E*)-1-phenyl-1, 3-butadiene **3a**.[6] The dihydroxylation occurred smoothly which resulted in a slightly greater preference for the internal double bond with a ratio of 2.2 to 1 and an ee of 95% for the major product **3b**, when phthalazine ligands were used (Scheme 2). We rationalized this 'disruption of conjugation' due to the preference of the

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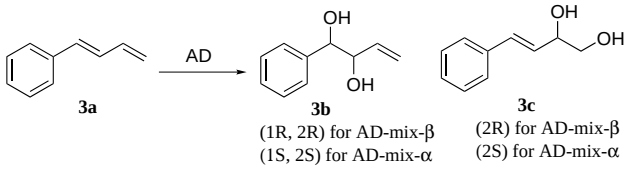
phthalazine ligands for trans-disubstituted double bond to terminal double bond. Moreover, when the general phthalazine ligands were changed to the terminal double bond preferred pyridine ligands[5d] without addition the usual used additive of methyl sulfonyl amide, the asymmetric dihydroxylation proceeded in the result of a moderate preference for oxidation of the outer terminal double bond with the ratio of 1:2.5 without remarkable decrease in the ee for both compounds **3b** and **3c** (Table).[7] In conclusion, these different results obtained could be tentatively rationalized in term of the presence of the terminal double bond of substrate **3a**.

Asymmetric dihydroxylation of (*E*)-1-phenyl-1, 3-butadiene using the phthalazine and pyridine ligands (Scheme 2, Table).



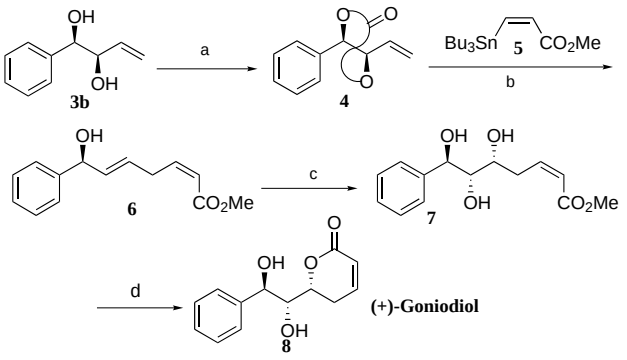
Scheme 2

Table

Ligands	Yield	**3b**:**3c** (Ratio)	**3b**, **3c** (ee, %)
$(DHQ)_2$-PHAL	83%	2.3:1	95, 91
$(DHQD)_2$-PHAL	84%	2.2:1	96, 91
$(DHQ)_2$-PYR	81%	1:2.5	92, 91
$(DHQD)_2$-PYR	81%	1:2.3	92, 90

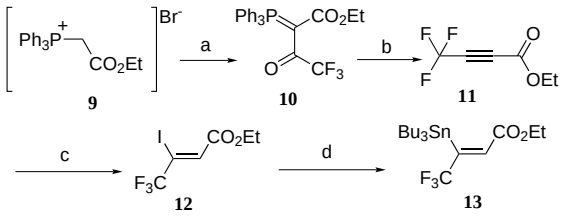
Protection of the diol **3b** with triphosgene furnished in nearly quantitative yield of **4**. Then the allylic cyclic carbonate **4** was coupled with (*Z*)-vinyltributylstannane **5**[8] in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%) according to the known protocol[9] to afford the (*E*)-substituted-allylic alcohol **6**, where the chemo-selectivity of *E* to *Z* is 97.2:2.8.[10] Dihydroxylation of **6** with Sharpless AD-mix-β furnished the triol **7** with high yield and high diastereoselectivity (de 96:4). Finally, acidic treatment the compound **7** resulted in the lactone formation to provide the natural product (+)-goniodiol **8** with an overall yield of 46% in 5 steps. To the best of our knowledge, this is probably the shortest asymmetric route to goniodiol **8** (Scheme 3).

Trifluoromethylated molecules often confer significant changes in their chemical and physical properties.[11] Upon the completion of goniodiol **8**, we plan to synthesize its β-trifluoromethyl derivatives by changing the vinyltributylstananne **5** to (*Z*)-β-trifluoromethyl -substituted vinyltributylstananne **13** in the palladium catalyzed coupling of cyclic allylic carbonate with vinyltributylstananne. The synthesis of **13** was started from ethyl 4,4,4-trifluoro-2-butynoate **11**, which is easily prepared from compound **9**



Scheme 3 Reagents and conditions: a) triphosgene, Et_3N, CH_2Cl_2, 0 °C, 2 h, 98%; b) $PdCl_2(CH_3CN)_2$ (5 mol%), 1.2 equiv **5**, DMF/H_2O (4:1), 0 °C, 1 h, 71%; c) AD-mix-β, 83%; d) PTS, toluene, 80 °C, 84%.

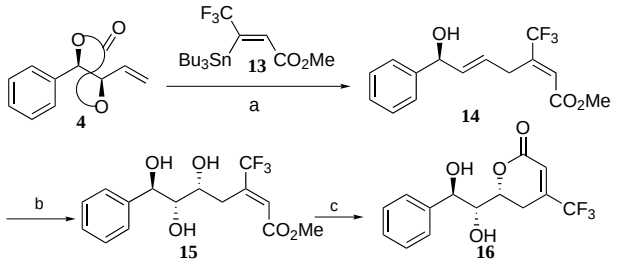
in two steps procedure.[12] Then, 3-iodo-4,4,4-trifluo-2-(*Z*)-butenoate **12** was prepared by reaction of **11** with sodium iodide in a sealed tube below 70 °C with 75% isolated yield according to literature.[13] Finally, addition of **12** to the solution of Bu_3SnCl in DMAC in the presence of activated zinc dust afforded the building block **13** (Scheme 4).



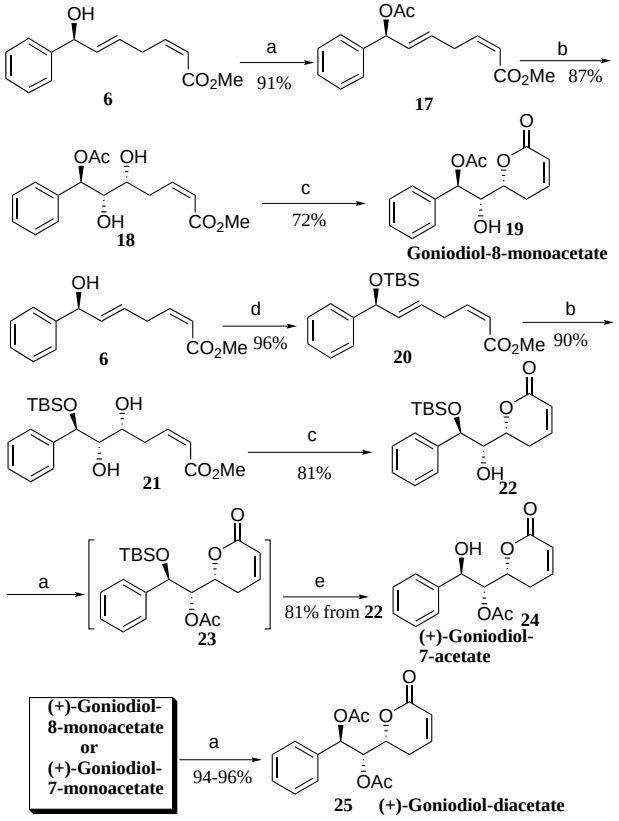
Scheme 4 Reagents and conditions: a) Et_3N, $(CF_3CO)_2O$, 0 °C, 2 h, 90%; b) Δ, 150–220 °C, 88%; c) CH_3CN, NaI, <70 °C, 6 h, 75%; d) Bu_3SnCl, Zn, DMAC, r.t., 2 h, 83%.

Palladium-catalyzed cross-coupling of cyclic carbonate **4** with the trifluoromethylated building block **13** provided the alcohol **14** with the yield of 51%. As the trifluoromethyl group possesses powerful electron-withdrawing ability, the coupling reaction was taken place under prolonged reaction time and loaded amount of catalyst with lower yield, compared to that of (*Z*)-vinyltributylstannane **5** as substrate. Finally, dihydroxylation of compound **14** followed by acid assisted lactonization afforded β-trifluoromethylgoniodiol **16**[14] in the same manner as described in the synthesis of (+)-goniodiol with the overall yield of 31% in three steps from compound **4** (Scheme 5).

(+)-Goniodiol-8-monoacetate, (+)-goniodiol-7-monoacetate and (+)-goniodioldiacetate were isolated from the leaves of *Goniothalamus amuyon* in 1992,[15] belonging to acetate derivatives of (+)-goniodiol. Simple acetylation of (+)-goniodiol with acetic anhydride always resulted in formation of a mixture of them.[16] We described herein an efficient route to synthesize them independently (Scheme 6).



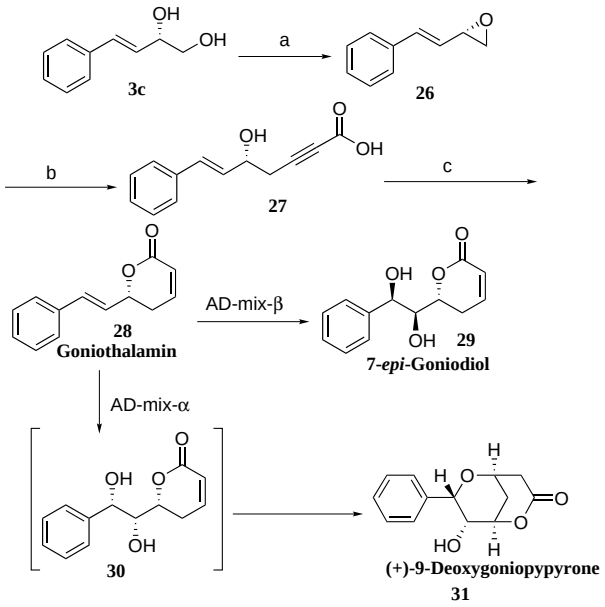
Scheme 5 Reagents and conditions: a) $PdCl_2(CH_3CN)_2$ (10 mol%), 1.5 equiv **13**, DMF/H_2O, r.t., 12 h, 51%; b) AD-mix-β, 81%; c) PTS, toluene, 80 °C, 83%.



Scheme 6 Reagents and conditions: a) Ac_2O, Et_3N, cat. DMAP, 0 °C, 1 h; b) AD-mix-β, 0 °C, 16 h; c) PTS, toluene, 80 °C; d) TBSCl, Et_3N, DMF, r.t., 6 h, 91%; e) TBAF, THF, r.t.

Protection the C_7-OH of **6** with Ac and TBS, followed by Sharpless AD-mix-β dihydroxylation provided the compound **18** and **21**, respectively, with high diastereoselectivity (de 95:5). (+)-Goniodiol-8-monoacetate **19** and compound **22** were obtained via acid assisted lactonization in the same manner as described in (+)-goniodiol. Protection of the 7-OH of compound **22** with Ac followed by deprotection the TBS protection group provided the sole natural product (+)-goniodiol-7-monoacetate **24**. Finally, treatment of either (+)-goniodiol-7-monoacetate or (+)-goniodiol-8-monoacetate with access acetic anhydride gave (+)-goniodioldiacetate **25** successfully.

After completion of (+)-goniodiol and its acetates and β-trifluoromethyl substituted derivatives, our interests were concerned on the asymmetric synthesis of 7-*epi*-Goniodiol **29** and (+)-9-deoxygoniopypyrone **31**.[2b,17] The synthesis started with compound **3c**, the other product of asymmetric dihydroxylation of (*E*)-1-phenyl-1, 3-butadiene (Scheme 7).



Scheme 7 Reagents and conditions: a) (1) TsCl, Pyridine, –30 °C, (2) K_2CO_3, MeOH, r.t., 40 min, 83% in two steps; b) propiolic acid, LDA (2 equiv), –78 °C to r.t., 94%; c) (1), Lindlar reduction, (2), PTS, toluene, 80 °C, 81% in two steps.

The diol **3c** was efficiently converted into the terminal epoxide **26** in two steps by initial treatment with *p*-toluenesulfonyl chloride followed by stirring with K_2CO_3 in MeOH with the overall yield of 83%. The epoxide **26** was added to a dianion generated from propiolic acid and LDA to yield an acid **27** with the yield of 94%. Lindlar reduction of **27** was followed by lactonization to give goniothalamin **28**. To our delight, the substrate Goniothalamin matches phthalazine ligands very well in both AD-mix-α reaction and AD-mix-β reaction. Dihydroxylation of goniothalamin **28** with AD-mix-β reaction ocurred smoothly to give the natural product 7-*epi*-goniodiol **29** with the yield of 87% and 96:4 de. In addition, Dihydroxylation of goniothalamin **28** with the AD-mix-α reaction directly gave the natural product 9-deoxygoniopypyrone **31** with the yield of 84% and 94:6 de, although compound **30** is an isolable compound which maybe due to the in situ heteroatom-Michael addition followed by the asymmetric dihydroxylation reaction.

In summary, we have shown herein a short and general route to total synthesis of styryllactones: (+)-goniodiols, 7-*epi*-goniodiol and 9-deoxygoniopypyrone using the asymmetric hydroxylation and the Pd(0)-catalyzed cross-coupling of allylic carbonate with vinyltributylstannane as the key steps.

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3b (1-Phenyl-but-3-ene-1,2-diol) for (1*S*, 2*S*): $[\alpha]_D^{20}$ –9.7 to 10.3 (*c* 0.7, $CHCl_3$). **(1*R*, 2*R*)**: $[\alpha]_D^{20}$ +10.6 to 11.1 (*c* 0.3, $CHCl_3$). IR (neat): 3390, 3087, 3032, 1645, 1604, 1495, 1454, 1198, 1126, 1054, 997, 928, 843, 763 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (s, 5 H), 5.7 (m, 1 H), 5.25 (dd, *J* = 3.0 Hz, *J* = 15.8 Hz, 1 H), 5.15 (dd. *J* = 3 Hz, *J* = 10 Hz, 1 H), 4.5 (d, *J* = 7 Hz, 1 H), 4.2 (m, ???H), 3.0 (s, 1 H), 2.7 (s, 1 H). MS (EI): *m/z* = 164 (M, 7.88), 146 (M – 18, 1.50), 114 (71.83), 107(100), 79 (68.72). HRMS for $C_{10}H_{12}O_2$: 164.0838. E. A for $C_{10}H_{12}O_2$: C, 72.99%; H, 7.27%.

3c (4-Phenyl-but-3-ene-1,2-diol) for (2*R*): $[\alpha]_D^{24}$ –38.4 (*c* 1.8, $CHCl_3$). **(2*S*)**: $[\alpha]_D^{24}$ +36.4 (*c* 1.45, $CHCl_3$). IR (neat): 3341, 3066, 3036, 1638, 1495, 1128, 1087, 942, 813, 751 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 5 H), 5,74 (d, 1 H, *J* = 12.6 Hz), 5.87 (dd, 1 H, *J* = 12.6 Hz, *J* = 7.4 Hz), 4.26 (m, 1 H), 3.75 (d, 2 H, *J* = 6.5 Hz), 3.1 (br, s, 1 H), 2.6 (br, s, 1 H). MS (EI) *m/z* = 164 (M, 7.88), 146 (M – 18, 1.50), 114 (71.83), 91(100), 79 (68.72). HRMS: Calcd for $C_{10}H_{12}O_2$: 164.0838. E. A. for $C_{10}H_{12}O_2$: C, 72.92%; H, 7.18%.

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(14) **16, β-Trifluoromethylgoniodiol**: $[\alpha]_D^{20}$ +68.2 (*c* 1.0, $CHCl_3$). MS (EI): *m/z*: 326 (M^+ + 23). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.3–7.5 (m, 5 H), 6.4 (s, 1 H), 5.3 (d, *J* = 7.2 Hz, 1 H), 4.8 (dd, *J* = 7.2, 5.8 Hz, 1 H), 4.2 (m, 1 H).

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