A Concise Synthesis of (+)-Goniodiol Using a Catalytic Hetero Diels–Alder/ Allylboration Sequence

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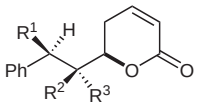
Abstract: A new short and efficient synthesis of (+)-goniodiol is reported using a catalytic asymmetric hetero Diels–Alder/allylboration sequence.

Key words: asymmetric catalysis, hetero Diels–Alder, allylboration reaction, (+)-goniodiol

The extracts from leaves of *Goniothalamus* species (Annonaceae) growing in Asia and India have been employed in traditional medicine for the treatment, in particular, of edema and rheumatism.[1] Several classes of bioactive compounds have been isolated from these plants including acetogenins[2] and alkaloids.[3] From an ethanolic extract of stem bark of *Goniothalamus giganteus*, McLaughlin et al. have found a new family of cytotoxic compounds, styryllactones.[4] To date, more than thirty bioactive molecules belonging to this family were listed from other *Goniothalamus* species.[5] Styryllactones can be divided in two main groups according to the size of the lactone ring (γ- and δ-lactones).

Among molecules having a six-membered lactone functionality, some of them were found to be significantly and selectively cytotoxic against several human tumors. For example, (+)-goniodiol exhibits toxicity against the human lung carcinoma cell line A-549 (ED_{50} = 0.122 μg mL^{-1}), whilst showing no such effects in a brine shrimp assay (LC_{50} > 500 μg mL^{-1}).[6] This natural product contains a 5,6-dihydro-2*H*-pyran-2-one unit with three contiguous stereocenters, structural core common to other styryllactones such as (+)-7-*epi*-goniodiol[7] and (+)-8-methoxygoniodiol[8] as shown in Figure 1.

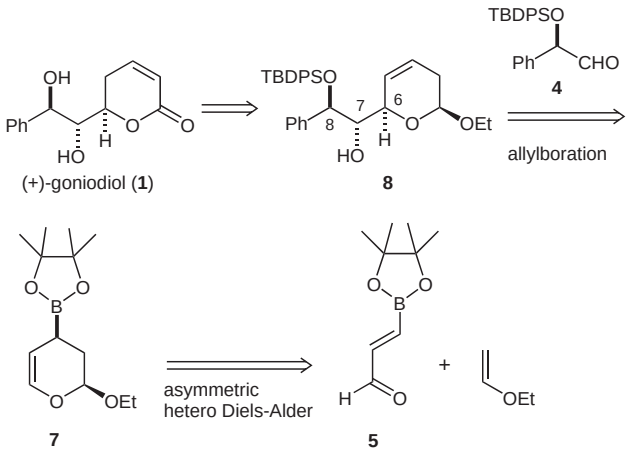


R^1 = OH, R^2 = H, R^3 = OH
(+)-goniodiol (**1**)
R^1 = OH, R^2 = OH, R^3 = H
(+)-7-*epi*-goniodiol (**2**)
R^1 = OCH_3, R^2 = H, R^3 = OH
(+)- 8-methoxygoniodiol (**3**)

Figure 1

Owing to its potent biological activity and the fact that it can be further converted to other styryllactones, several methods have been reported for the synthesis of (+)-goniodiol. Most of the synthetic strategies start from chiral products[9] such as (*R*)-mandelic acid[9c] and 2,3-*O*-isopropylidene-D-glyceraldehyde.[9d] Other approaches employing stoichiometric and catalytic asymmetric reactions as key steps for the creation of the chiral centers have been described.[10] Herein, we report a concise synthesis of (+)-goniodiol using a tandem reaction which can also be useful for the preparation of other stereoisomers and the design of analogues.

Recently, we and others have simultaneously developed a general method for the introduction of an hydroxyalkyl group adjacent to the heteroatom in dihydropyran ring systems using a catalytic asymmetric hetero Diels–Alder/ allylboration sequence.[11] We envisioned that the cyclic allylboronate **7**, obtained by the asymmetric inverse electron demand cycloaddition between ethyl vinyl ether and heterodiene **5**, could react with a conveniently protected aldehyde derived from (*R*)-mandelic acid **4** to give the intermediate **8** with control of configuration at C-6, C-7 and C-8. Oxidation of acetal followed by migration of the double bond would lead to the α,β-unsaturated δ-lactone skeleton of (+)-goniodiol as depicted in Scheme 1.



Scheme 1 Retrosynthetic analysis.

(*R*)-(*tert*-Butyldiphenylsilanyloxy)phenylacetaldehyde (**4**) was prepared in three steps from (*R*)-mandelic acid. After esterification with methanol in the presence of *p*-TsOH, the silylation of the hydroxy group with *t*-$BuPh_2SiCl$ and imidazole followed by the reduction of ester function with *i*-Bu_2AlH at –78 °C led to the expected O-silylated mandelic aldehyde **4** in 77.2% overall yield (Scheme 2). The

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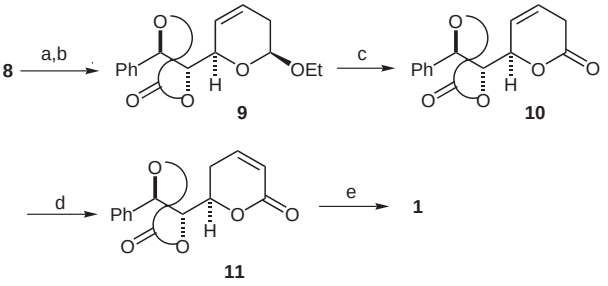
adduct **7** is the result of an hetero Diels–Alder reaction between ethyl vinyl ether and (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enal (**5**)[12] which is easily prepared from propionaldehyde diethyl acetal. When the reaction is catalyzed with Jacobsen's chiral Cr(III) complex **6**[13] and a dehydrating agent, cyclic allylboronate **7** was obtained in 85% yield with a high diastereo- and enantiomeric purity (>95% de, 96% ee). The allylboration reaction between **7** and **4** (2 equiv) can be performed in toluene at 70 °C for 48 hours to give the dihydropyran **8** in 78% yield, as unique stereoisomer.[14] However, in order to decrease the time of the reaction and quantity of aldehyde used, reaction was carried out without solvent. After ten hours at 70 °C and using only one equivalent of **4**, compound **8** was obtained in 65% yield that is still acceptable taking into account the high level of stereoselectivity of this reaction.[15]

This hetero Diels–Alder/allylboration process could be performed in one pot without purification of **7**.[11c] However, since the chiral catalyst can influence the diastereoselectivity of the allylboration, we chose to carry out the reaction sequence in two steps. It is worthy to note that, to our knowledge, it is the first example of allylboration involving a chiral cyclic γ-alkoxy-allylboronate and a chiral aldehyde described in the literature.[16]

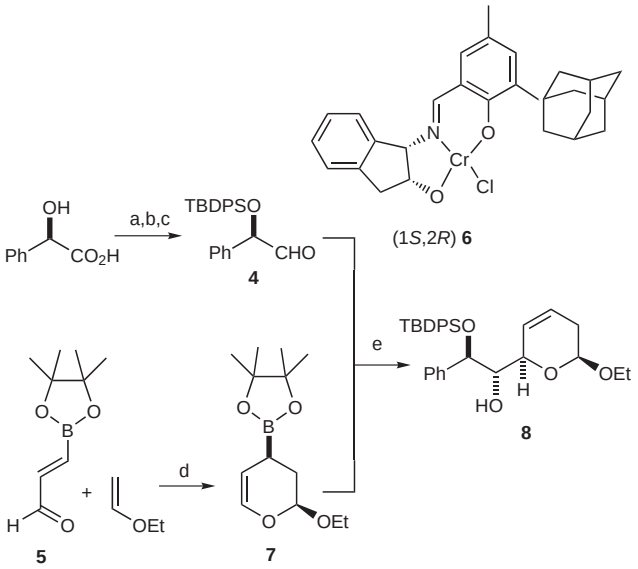
Deprotection of the TBDPS group with TBAF, followed by a treatment with triphosgene in the presence of pyridine provided the cyclic carbonate **9** in 85.5% yield for the two steps (Scheme 3). The direct one-step conversion of the lactol to the corresponding lactone using one equivalent of *m*-CPBA with boron trifluoride etherate[17] could not be carried out cleanly. Therefore, lactone **10** was obtained in two steps (60%), after hydrolysis of the cyclic hemiacetal followed by oxidation. Conversion of **10** into the corresponding α,β-unsaturated δ-lactone **11** was achieved in 90% yield by isomerization of the double bond using a catalytic amount of DBU at room temperature. Unfortunately, deprotection of the 1,2-diol under various basic conditions (0.5 N NaOH,[18] 0.25 N MeONa[19]), followed by a treatment with trifluoroacetic acid failed to give the expected (+)-goniodiol. In all cases, a complex mixture of products was obtained. We also attempted acidic conditions to cleave the cyclic carbonate. When **11** is warmed at reflux for six hours in MeOH with 6 N HCl, (+)-goniodiol was obtained in a poor yield (20%) with spectral properties identical to those reported in the literature.[4,9c]



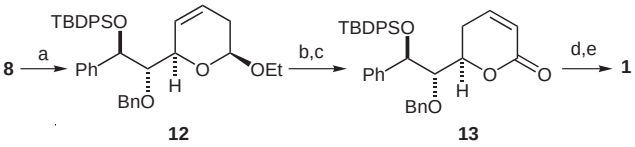
Scheme 3 *Reagents and conditions*: (a) TBAF (1.5 equiv), THF, r.t., 3 h, 90%; (b) triphosgene (0.5 equiv), pyridine, CH_2Cl_2, –70 °C, 0.1 h, 95%; (c) (i) 6 N HCl, THF, r.t., 12 h; (ii) PDC (1.1 equiv), AcONa (1.1 equiv), 4 Å MS, CH_2Cl_2, r.t., 48 h, 60% overall yield; (d) DBU (0.01 equiv), THF, r.t., 12 h, 90%; (e) 6 N HCl, MeOH, reflux, 6 h, 20%.

To improve the overall yield, we planned a new synthesis of (+)-goniodiol via intermediate **8** using benzyl ether as protecting group to the alcohol (Scheme 4). Reaction of **8** with excess BnBr/NaH in the presence of a catalytic amount of $Bu_4N^+I^-$ gave its *O*-benzyl derivative **12** in 84% yield. The use of *m*-CPBA/$BF_3{\cdot}OEt_2$ system led successfully to the formation of the corresponding lactone. Treatment with DBU in CH_2Cl_2 at room temperature afforded the α-pyrone **13** in 82% yield for the last two steps. Finally, cleavage of protecting groups, desilylation with HF/pyridine and debenzylation with $TiCl_4$, yielded (+)-goniodiol (**1**) which was thus obtained in 27% overall yield instead of 9.2% starting from the advanced intermediate **8**.[20]

In summary, (+)-goniodiol has been synthesized in 7 steps and in 15% overall yield from (2*E*)-3-borylacrolein **5** using a strategy based on an asymmetric three-component hetero Diels–Alder/allylboration sequence. The ready



Scheme 2 *Reagents and conditions*: (a) MeOH, *p*-TsOH (0.01 equiv), reflux, 3 h, quantitative yield; (b) *t*-$BuPh_2SiCl$ (1.5 equiv), imidazole (2 equiv), DMAP (0.05 equiv), CH_2Cl_2, r.t., 12 h, 93%; (c) *i*-Bu_2AlH (1.1 equiv), Et_2O, –78 °C, 0.5 h, 83%; (d) **6** (0.05 equiv), 4 Å MS, r.t., 2 h, 85%; (e) 70 °C, 10 h, 65%.



Scheme 4 *Reagents and conditions*: (a) NaH (1.3 equiv), BnBr (1.5 equiv), $Bu_4N^+I^-$ (0.1 equiv), THF, r.t., 3 h, 84%; (b) *m*-CPBA (1.5 equiv), $BF_3{\cdot}OEt_2$ (1.5 equiv), CH_2Cl_2, 0 °C to r.t., 14 h, 90%; (c) DBU (0.01 equiv), THF, r.t., 18 h, 91%; (d) HF/pyridine, r.t., 48 h, 50%; (e) $TiCl_4$ (2 equiv), CH_2Cl_2, r.t., 1 h, 78%.

availability of both isomers of mandelic acid and chromium(III) complex, makes this procedure especially attractive for the synthesis of stereoisomers of (+)-goniodiol. Application of this methodology to the preparation of other natural styryllactones is currently underway at the laboratory.

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(14) The absolute configuration of the four stereocenters was confirmed by the examination of its X-ray crystal structure. See ref. 11b.

(15) At this temperature, we observed a slow transformation of aldehyde **4** into benzaldehyde.

(16) The stereoselectivity of **7** has been studied with various chiral aldehydes. These results will be reported elsewhere.

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(20) All new compounds were fully characterized (^{1}H NMR, ^{13}C NMR, elemental analysis or HRMS).
Compound **9**: $[\alpha]_D^{20}$ –145.9 (*c* 1.11, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.1 Hz), 2.12 (m, 2 H), 3.33 (dq, 1 H, *J* = 7.1, 9.5 Hz), 3.80 (dq, 1 H, *J* = 7.1, 9.0 Hz), 4.09 (m, 1 H), 4.40 (dd, 1 H, *J* = 3.6, 7.4 Hz), 4.92 (dd, 1 H, *J* = 3.8, 7.8 Hz), 5.34 (m, 1 H), 5.79 (m, 1 H), 5.82 (d, 1 H, *J* = 7.8 Hz), 7.32 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 30.5, 64.2, 71.8, 79.7, 80.8, 98.0, 123.5, 127.2, 126.3, 128.5, 129.1, 132.9, 154.5. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.22; H, 6.33.
Compound **11**: $[\alpha]_D^{20}$ –144.3 (*c* 0.62, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (m, 1 H), 2.70 (m, 1 H), 4.15 (ddd, 1 H, *J* = 1.1, 3.8, 12.8 Hz), 4.98 (dd, 1 H, *J* = 1.1, 8.1 Hz), 5.87 (dd, 1 H, *J* = 2.3, 9.9 Hz), 5.98 (d, 1 H, *J* = 8.1 Hz), 6.85 (ddd, 1 H, *J* = 2.1, 6.4, 9.9 Hz), 7.48 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 72.8, 78.0, 79.2, 119.7, 123.7, 125.3, 127.7, 128.4, 130.4, 153.0, 160.8. Anal. Calcd for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.46; H, 4.60.
Compound **12**: $[\alpha]_D^{20}$ +64.1 (*c* 0.32, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 9 H), 1.18 (t, 3 H, *J* = 7.1 Hz), 2.05–2.30 (m, 2 H), 3.22 (dq, 1 H, *J* = 7.1, 9.5 Hz), 3.70 (m, 1 H), 4.23 (d, 1 H, *J* = 11.1 Hz), 4.35 (d, 1 H, *J* = 11.1 Hz), 4.44 (dd, 1 H, *J* = 3.2, 8.4 Hz), 4.67 (m, 1 H), 5.02 (d, 1 H, *J* = 6.7 Hz), 5.52 (dd, 1 H, *J* = 1.2, 9.8 Hz), 7.00–7.55 (m, 16 H), 7.67 (m, 2 H), 7.76 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 19.4, 26.9, 27.1, 31.4, 63.7, 74.4, 74.6, 75.1, 85.0, 98.7, 124.4, 127.2, 127.3, 127.4, 127.5, 127.7, 127.9, 128.1, 128.6, 129.4, 129.5, 129.6, 133.4, 134.0, 134.8, 136.0, 136.1, 138.6, 141.2. HRMS (ES): *m/z* calcd for $C_{38}H_{44}O_4Si$ $[M + Na]^+$: 615.2907; found: 615.2902.
Compound **13**: $[\alpha]_D^{20}$ +45.9 (*c* 1.82, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 2.00 (ddd, 1 H, *J* = 3.7, 6.2, 18.1 Hz), 2.42 (m, 1 H), 3.58 (dd, 1 H, *J* = 2.5, 7.8 Hz), 3.90 (d, 1 H, *J* = 18.4 Hz), 3.95 (d, 1 H, *J* = 18.4 Hz), 4.76 (td, 1 H, *J* = 3.0, 12.6 Hz), 5.11 (d, 1 H, *J* = 7.8 Hz), 5.89 (dd, 1 H, *J* = 2.4, 9.8 Hz), 6.75 (ddd, 1 H, *J* = 2.1, 6.2, 9.8 Hz), 7.01 (m, 2 H), 7.19–7.68 (m, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 26.1, 27.1, 74.1, 74.5, 76.3, 83.9, 121.1, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 129.5, 129.7, 133.1, 133.5, 135.9, 136.0, 137.6, 141.3, 144.8, 163.5. HRMS (ES): *m/z* calcd for $C_{36}H_{38}O_4Si$ $[M + Na]^+$: 585.2437; found: 585.2434.