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First synthesis of (+)-8-methoxygoniodiol and its analogue, 8-deoxygoniodiol, using a three component strategy

François Carreaux,[a,*] Annaick Favre,[a] Bertrand Carboni,[a] Isabelle Rouaud[b] and Joel Boustie[b]

[a]*Ingéniérie chimique et molécules pour le vivant, UMR 6226 CNRS-Université de Rennes 1, 35042 Rennes cedex, France*
[b]*EA Subtances lichéniques et Photoprotection, Université de Rennes 1, 2 avenue du professeur Léon Bernard, 35043 Rennes cedex, France*

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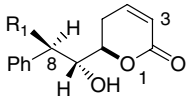
Abstract—We have described the first total synthesis of the natural product, (+)-8-methoxygoniodiol, and its analogue, 8-deoxygoniodiol using a catalytic asymmetric hetero-Diels–Alder/allylboration sequence involving three partners. The cytotoxic activity of these final compounds and of two synthetic intermediates has been evaluated against human cancer cell lines (A375P and A375M), showing the importance of the lactone moiety.

Asian trees of the genus *Goniothalamus* have been a source of numerous families of compounds possessing interesting biological properties including alkaloids,[1] styryllactones[2] and acetogenins.[3] For example, some styryllactones isolated from an ethanolic extract of stem bark of *Goniothalamus giganteus* such as (+)-Goniodiol **1**, show potent and cytotoxic activities against several human tumors.[4] Consequently, there have been important synthetic efforts toward **1** resulting in the number of total syntheses.[5] However, there have been few reports concerning the synthesis and biological evaluation of structural analogues due to the lack of flexible and versatile access to this class of compounds.[5g]

Recently, new members of the natural styryllactones have been reported from *Goniothalamus amuyon*.[6] The structure and absolute stereochemistry of one of these compounds, **1a**, have been established as being similar with those of (+)-goniodiol, except for the presence of a methoxy group at C-8 as shown in Figure 1. Therefore, the trivial name of 8-methoxygoniodiol was assigned to this compound.[7] In spite of this structural similarity, **1a** exhibited a very different cytotoxicity from



R_1= OH, (+)-goniodiol, **1**
R_1= OMe, (+)-8-methoxygoniodiol, **1a**
R_1= H, (+)-8-deoxygoniodiol, **1b**

Figure 1.

(+)-goniodiol, depending on the type of human cancer cell lines.[6] We thus thought that it would be important to be able to lay out some quantity of (+)-8-methoxygoniodiol to supplement its biological evaluation.[8] However, to the best of our knowledge, no synthesis of this natural product has been described to date. Herein, we report the first synthesis of this natural product using a three component strategy which is also useful for the design of analogues such as 8-deoxygoniodiol **1b**, including cytotoxicity against two A375 melanoma cell lines.

In the course of our program directed toward the discovery of new multicomponent reactions, we and others have simultaneously developed a general method for the asymmetric synthesis of α-hydroxyalkyl dihydropyrans using a catalytic inverse electron demand hetero-Diels–Alder (IEDHDA)/allylboration sequence.[9] We have recently employed this strategy with success in the synthesis of (+)-Goniodiol proving that it is possible to create three contiguous asymmetric centers in a high stereoselective manner using a chiral aldehyde in the allylboration step.[5i] In a similar way, we envisioned that this

Keywords: Natural product; Hetero-Diels–Alder; Allylboration reaction; Asymmetric catalysis; (+)-8-Methoxygoniodiol; 8-Deoxygoniodiol; Cytotoxicity.
* Corresponding author. Tel.: +33 2 23 23 57 34; e-mail: francois.carreaux@univ-rennes1.fr

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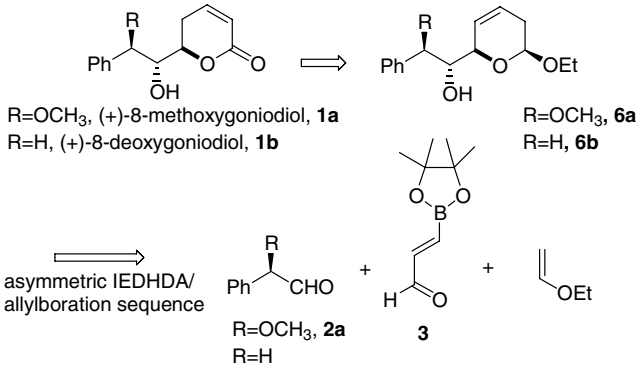
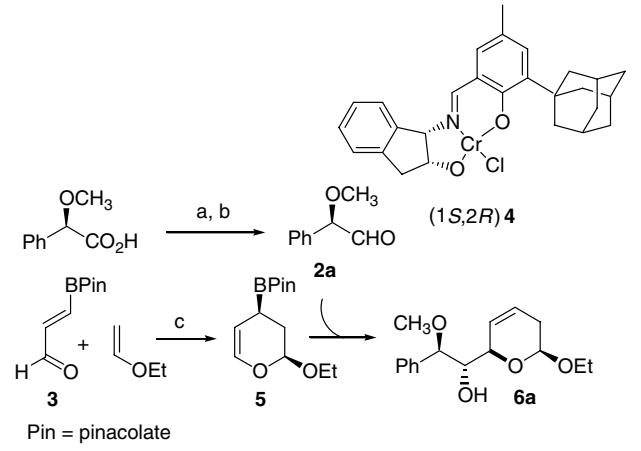
methodology could be employed for the synthesis of 8-methoxygoniodiol, via the key intermediate **6a**, using in the reactional sequence the following three partners: ethyl vinyl ether, (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enal **3**[10] and (2*R*)-methoxy(phenyl)acetaldehyde **2a**. Oxidation of protected lactol **6a** followed by migration of the double bond would lead to the α,β-unsaturated δ-lactone skeleton of **1a** as depicted in Scheme 1. This strategy should also allow us to synthesize 8-deoxygoniodiol **1b**, using phenylacetaldehyde in the IEDHDA/allylboration process. The preparation of this analogue was envisaged in order to determine the importance of the substituent at C-8 on biological activity.

Although the *O*-methylation of mandelic acid can be carried out without epimerization under certain conditions,[11] we chose to use the commercial (*R*)-*O*-methylmandelic acid as starting material for the synthesis of aldehyde **2a**. After esterification with methanol in the presence of *p*-TsOH, the reduction of the ester function with *i*-Bu_2AlH at −78 °C led to the expected *O*-methyl mandelic aldehyde with some impurities (Scheme 2). To preserve the enantiomeric purity, **2a** was directly used without further purification in the allylation reaction. The asymmetric synthesis of cyclic allylboronate **5** was achieved from ethyl vinyl ether and **3**, following an hetero-Diels–Alder reaction catalyzed with Jacobsen's chiral Cr(III) complex **4**.[12] After completion of the cycloaddition step, aldehyde **2a** is added and the mixture is warmed at 40 °C for 48 h to furnish intermediate **6a** in 60% yield. It should be noted that the presence of the chiral catalyst does not seem to have influence on the stereoselectivity of the allylboration reaction, since dihydropyran **6a** is obtained with the same diastereoselectivity (>95%) as without a catalyst.



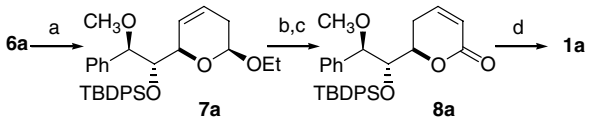
Scheme 1. Retrosynthetic analysis.



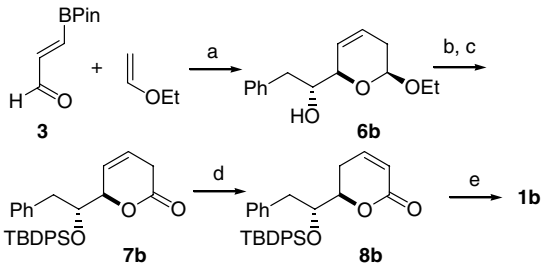
Scheme 2. Reagents and conditions: (a) MeOH, *p*-TsOH (0.01 equiv), reflux, 3 h, 84%; (b) *i*-Bu_2AlH (1.1 equiv), Et_2O, −78 °C, 0.5 h; (c) (i) **4** (0.01 equiv), 4 Å MS, rt, 2 h; (ii) **2a** (1.5 equiv), 40 °C, 48 h, 60%.

In order to reduce the number of steps of our synthesis, we first oxidized ethyl lactol **6a** into lactone without protecting the hydroxyl group, using a one pot procedure described by Grieco.[13] Unfortunately, under these conditions, we mainly obtained the bicyclic acetal product.[14] Treatment of **6a** with *t*-$BuPh_2SiCl$ in the presence of imidazole and DMAP gave the protected alcohol in 73% yield. The one pot conversion of **7a** into the corresponding lactone using *m*-CPBA (1.3 equiv) with boron trifluoride etherate was effected, in this case, cleanly in 90% yield. Isomerization of the double bond was realized with a catalytic amount of DBU in CH_2Cl_2 at room temperature to give the α,β-unsaturated δ-lactone **8a** in 80% yield. The natural product was obtained after desilylation with TBAF in 28.9% overall yield from the advanced intermediate **6a**. The spectroscopic data of synthetic (+)-8-methoxygoniodiol are in full agreement with previously published data.[6a] The specific rotation, $[\alpha]_D^{23}$ +26.4 (*c* 0.32, $CHCl_3$), was also in good agreement with that reported for the natural product, $[\alpha]_D^{25}$ +24.2 (*c* 0.68, $CHCl_3$) (Scheme 3).

The synthesis of 8-deoxygoniodiol began with the asymmetric catalyzed hetero-Diels–Alder/allylboration sequence using phenylacetaldehyde in place of *O*-methyl mandelic aldehyde. The tandem process was performed in 'one pot' and provided the desired pyran **6b** in 82% as single diastereoisomer in 96% enantiomeric excess.[9b] Silylation of the hydroxyl function using *tert*-butyldiphenylsilyl chloride, imidazole and DMAP provided **7b** in 93% yield. Surprisingly, conversion of **7b** into the corresponding lactone using the one pot procedure cited previously was achieved in a poor yield (32%). Therefore, lactone **7b** was obtained in two steps (76.5%), after hydrolysis of the ethyl lactol followed by oxidation. The final steps, isomerization of the double bond and of the silyl protective group, produced the desired product **1b**. 8-Deoxygoniodiol was thus synthesized in 29.4% yield from 3-boroacrolein pinacolate **3** (Scheme 4).[15]



Scheme 3. Reagents and conditions: (a) TBDPSCl (1.3 equiv), imidazole (2.4 equiv), DMAP (cat.), CH_2Cl_2, rt, 12 h, 73%; (b) *m*-CPBA (1.3 equiv), $BF_3{\cdot}OEt_2$ (1.3 equiv), CH_2Cl_2, 0 °C to rt, 15 h, 90%; (c) DBU (0.01 equiv), THF, 0 °C to rt, 20 h, 80%; (d) TBAF (1.1 equiv), THF, 0 °C, 2 h, 55%.



Scheme 4. Reagents and conditions: (a) (i) **4** (0.01 equiv), 4 Å MS, rt, 2 h; (ii) $PhCH_2CHO$ (2 equiv), 45 °C, 24 h, 82%; (b) TBDPSCl (1.3 equiv), imidazole (2.4 equiv), DMAP (cat.), CH_2Cl_2, rt, 18 h, 93%; (c) (i) 6 N HCl, THF, rt, 20 h, 85%; (ii) PDC (1.1 equiv), AcONa (1.1 equiv), 4 Å MS, rt, 24 h, 90%; (d) DBU (0.01 equiv), THF, 0 °C to rt, 20 h, 95%; (e) TBAF (1.1 equiv), THF, 0 °C to rt, 3 h, 53%.

Table 1. Cytotoxic Activity of 8-methoxygoniodiol **1a** and its analogues against cancer cell lines

Compound	A375P IC_{50}[a] (μM)	A375M IC_{50}[a] (μM)
1a	35.1 (±4.5)	75.7 (±11.8)
1b	36.9 (±3.9)	82.6 (±8.8)
6a	>100	>150
6b	>100	>200
5FU	20.6 (±5.9)	22.6 (±4.2)

[a] Values are means of three experiments, standard deviation is given in parentheses. 5FU = 5-Fluorouracile (standard).

The cytotoxicity of compounds **1a**, **1b**, **6a** and **6b** against low (A375P) and medium (A375M) metastatic human melanoma cell lines using the MTT assay[16] is reported in Table 1. These melanoma cell lines appear to be slightly less sensitive to 8-methoxygoniodiol **1a** than the Hep G2 and Hep 3B hepatic cell lines previously tested.[6b] However, **1a** is at least eightfold more active with respect to A375 cells compared to the NUGC (human gastric cancer) and HONE-1 (human nasopharyngeal carcinoma) cancer cell lines.[6a] Although cytotoxicity values are moderate, the 8-methoxy substituent does not appear to have any incidence on activity. On the contrary, the presence of the lactone ring is found to be necessary for the activity, since the corresponding 2-*O*-ethyl derivatives were shown to be dramatically less active.

In summary, the first total synthesis of (+)-8-methoxygoniodiol and its analogue, 8-deoxygoniodiol, was accomplished using a three component hetero-Diels–Alder/allylboration process. The route outlined above contains sufficient flexibility to provide additional analogues at C-8, and also at C-3 using substituted enol ether,[17] opening interesting perspectives for structure-activity relationship studies. Efforts in this area will be reported in due course.

Acknowledgements

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7. The IUPAC name of 8-deoxygoniodiol is (6*R*)-6-[(1*R*)-1-hydroxy-2-phenylethyl]-5,6-dihydro-2*H*-pyran-2-one.
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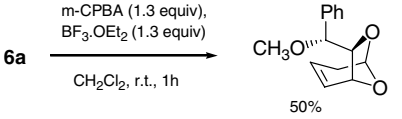
14. 

15. Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (^1H, ^{13}C NMR, elemental analysis or HRMS) consistent with their structures. For example, compound **6a**: $[\alpha]_D^{23}$ +67.8 (*c* 0.3, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$):

7.35–7.30 (m, 5H), 5.86 (m, 1H), 5.68 (dd, 1H, $J = 1.8$ and 10.1 Hz), 4.85 (dd, 1H, $J = 5.0$ and 5.6 Hz), 4.74 (d, 1H, $J = 1.8$ Hz), 4.28 (d, 1H, $J = 8.5$ Hz), 4.03 (dq, 1H, $J = 7.1$ and 9.5 Hz), 3.67 (m, 2H), 3.26 (s, 3H), 2.46 (d, 1H, $J = 8.1$ Hz), 2.30 (m, 2H), 1.31 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 139.5, 128.3, 128.0, 127.9, 127.4, 124.8, 98.3, 83.2, 75.6, 73.5, 64.5, 56.8, 30.9, 15.2. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.11; H, 8.02. Compound **7a**: $[\alpha]_D^{23}$ +66.7 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 (m, 2H), 7.62 (m, 2H), 7.51–7.28 (m, 11H), 5.22 (m, 1H), 5.06 (ddd, 1H, $J = 1.2$, 1.3 and 10.1 Hz), 4.42 (m, 2H), 4.20 (m, 2H), 3.89 (dq, 1H, $J = 7.1$ and 9.7 Hz), 3.43 (dq, 1H, $J = 7.1$ and 9.7 Hz), 3.17 (s, 3H), 2.09 (m, 1H), 1.96 (m, 1H), 1.25 (t, 3H, $J = 7.1$ Hz), 0.78 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 139.6, 136.3, 135.5, 134.5, 133.1, 129.5, 129.0, 127.9, 127.4, 127.0, 126.5, 124.0, 122.3, 99.5, 83.5, 77.0, 75.6, 62.3, 56.4, 31.4, 26.6, 19.5, 15.2. Anal. Calcd for $C_{32}H_{40}O_4Si$: C, 74.38; H, 7.80. Found: C, 74.45; H, 7.86. Compound **8a**: $[\alpha]_D^{23}$ +111.5 (*c* 0.48, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 7.69 (d, 2H, $J = 7.3$ Hz), 7.50 (d, 2H, $J = 7.6$ Hz), 7.52–7.23 (m, 11H), 6.56 (m, 1H), 5.86 (dd, 1H, $J = 2.1$ and 9.5 Hz), 4.76 (m, 1H), 4.54 (d, 1H, $J = 7.9$ Hz), 3.93 (d, 1H, $J = 7.9$ Hz), 3.16 (s, 3H), 2.29 (m, 1H), 1.56 (m, 1H), 0.63 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 164.1, 145.2, 139.2, 136.3, 133.8, 130.0, 129.5, 128.8, 128.5, 128.4, 127.7, 127.5, 120.9, 82.6, 76.8, 76.3, 56.5, 26.4, 26.2, 19.4. HRMS (EI): *m*/*z* Calcd for $C_{30}H_{34}O_4Si$ $[M]^+$: 486.2226. Found: 486.2229. Compound **7b**: Mp 114–116 °C. $[\alpha]_D^{23}$ −36.4 (*c* 0.34, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 7.74 (dd, 2H,$J = 1.6$ and 7.9 Hz), 7.63 (dd, 2H, $J = 1.5$ and 8.5 Hz), 7.56–7.35 (m, 6H), 7.22–7.11 (m, 3H), 6.85 (dd, 2H, $J = 2.6$ and 7.6 Hz), 5.93 (m, 1H), 5.72 (m, 1H), 4.69 (m, 1H), 3.97 (m, 1H), 3.19–3.02 (m, 3H), 2.63 (dd, 1H, $J = 5.2$ and 14.1 Hz), 1.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.9, 137.4, 136.1, 136.0, 135.9, 135.8, 133.4, 133.1, 130.1, 129.8, 129.6, 128.4, 127.9, 127.7, 126.4, 124.0, 123.0, 79.1, 76.2, 38.9, 30.3, 26.9, 19.4. HRMS (EI): *m*/*z* Calcd for $C_{29}H_{32}O_3Si$ $[M]^+$: 456.2121. Found 456.2132. Compound **8b**: $[\alpha]_D^{23}$ −33.1 (*c* 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (dd, 2H, $J = 1.4$ and 6.5 Hz), 7.64 (dd, 2H, $J = 1.4$ and 7.8 Hz), 7.57–7.38 (m, 6H), 7.22–7.11 (m, 3H), 6.91 (dd, 2H, $J = 2.3$ and 7.6 Hz), 6.85 (m, 1H), 5.97 (dd, 1H, $J = 2.4$ and 9.7 Hz), 4.11 (m, 1H), 3.94 (m, 1H), 3.23 (dd, 1H, $J = 8.7$ and 13 Hz), 2.80–2.66 (m, 2H), 2.06 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 164.3, 145.5, 137.5, 136.1, 136.0, 135.9, 133.3, 133.2, 130.1, 129.8, 129.6, 129.5, 128.5, 128.4, 127.9, 127.7, 126.4, 121.1, 76.9, 75.5, 38.8, 27.0, 25.6, 19.5. HRMS (EI): *m*/*z* Calcd for $C_{29}H_{32}O_3Si$ $[M]^+$: 456.2121. Found 456.2129. Compound **1b**: $[\alpha]_D^{23}$ +19.4 (*c* 0.28, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 7.44–7.18 (m, 5H), 6.95 (ddd, 1H, $J = 1.9$, 6.3 and 9.7 Hz), 6.05 (dd, 1H, $J = 2.7$ and 9.7 Hz), 4.40 (dt, 1H, $J = 3.4$ and 12.7 Hz), 3.89 (m, 1H), 2.99 (m, 2H), 2.75 (m, 1H), 2.25 (ddd, 1H, $J = 3.8$, 6.2 and 18.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 164.4, 145.7, 137.2, 129.4, 128.7, 126.8, 120.9, 78.5, 73.4, 39.3, 25.9. HRMS (EI): *m*/*z* Calcd for $C_{13}H_{14}O_3$ $[M]^+$: 218.0943. Found 218.0958.

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