JOC*Note*

Stereoselective Syntheses of (+)-Goniodiol, (−)-8-Epigoniodiol, and (+)-9-Deoxygoniopypyrone via Alkoxyallylboration and Ring-Closing Metathesis

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Abstract: A convenient synthesis of (+)-goniodiol, (−)-8-epigoniodiol, and (+)-9-deoxygoniopypyrone has been developed via asymmetric alkoxyallylboration and ring-closing metathesis pathways.

5,6-Dihydro-2*H*-pyran-2-ones (α-pyrones) are present in a large number of biologically active organic molecules.[1] Examples of such molecules include fostreicin,[2] pironetin,[3] passifloricins,[4] and cryptopyranmoscatones.[5] α-Pyrones have been utilized as intermediates for synthetic transformations.[6] Once the asymmetric center is introduced, it can be used to induce stereospecificity to the neighboring carbons in a variety of optically active molecules via substrate-controlled reactions.[6]

Goniopyrones, a series of styryllactones, isolated from various species of the genus *Goniothalamus* (Figure 1),[7] have been traditionally used for the treatment of edema and rheumatism.[8] Other general applications include

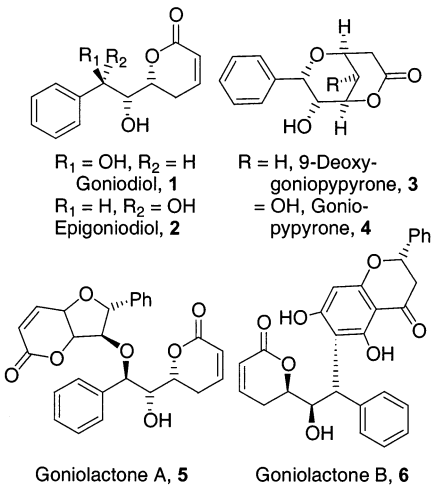

FIGURE 1.

their use as painkillers[9] and mosquito repellants.[7b] Several of these styryllactones have also been found to possess excellent antitumoral properties.[7d−f,10]

Due to the broad spectrum of pharmacological properties associated with these molecules, several syntheses have been reported in the literature.[11,12] For example, Ley and co-workers have recently reported the synthesis of (+)-goniodiol via a Lewis acid-mediated diastereoselective oxygen-to-carbon rearrangement of an anomerically linked silyl enol ether.[12f] Tsubuki et al. have described a stereocontrolled synthesis of several styryllactones start-

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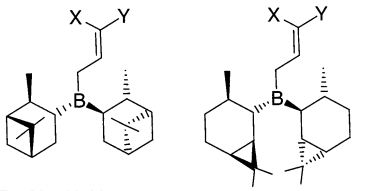


FIGURE 2.

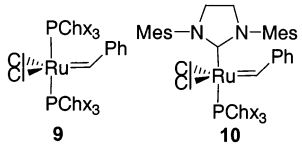
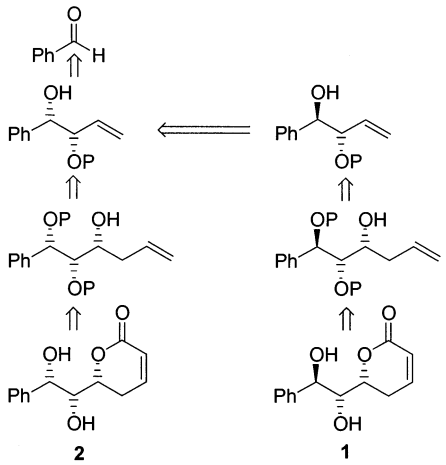


FIGURE 3.

ing from 2,3-*O*-isopropylidene-D-glyceraldehyde employing NBS-mediated lactol formation, followed by chemoselective phenyl addition using triisopropoxyphenyltitanium,[12i] and Vatele and Surivet have synthesized enantiopure styryllactones starting from a common chiral precursor ethyl-4-(*tert*-butyldimethylsilyloxy)-2,3-isopropylidinedioxy-4-phenylbutanoate, prepared from (*R*)-mandelic acid.[12j]

As part of our program on the synthesis of biologically active natural products[13] via pinane-based versatile reagents,[14] we undertook the synthesis of styryllactones. Although asymmetric allyl- and crotylboration using terpenes as chiral auxiliaries have been well exploited for organic syntheses[15] (Figure 2), the corresponding alkoxyallylboration[16] has received little attention.[16b−f] We envisaged alkoxyallylboration and ring-closing metathesis[17] reactions using Grubbs' catalysts (Figure 3) as the most appropriate sequence for a short synthesis of styryllactones. The alkoxy moiety in the alkoxyallylboranes proved to be crucial for the achievement of the synthesis. Herein we discuss our successful synthesis of styryllactones.

SCHEME 1



We began with the synthesis of (+)-goniodiol (**1**) and (−)-8-epigoniodiol (**2**). In addition to the α-pyrone unit, **1** possesses an anti diol and **2** possesses a syn diol unit on the side chain. Our retrosynthetic analysis is shown in Scheme 1.

As can be seen, we chose the syn homoallylic diol for the synthesis of both **1** and **2**. One of the chiral centers was inverted for the synthesis of **1**. We explored the possibility of utilizing α-pinene-based asymmetric alkoxyallylboration due to the demonstrated capability of these reagents in affording monoprotected syn diols with excellent diastereo- and enantioselectivities. With this in mind, we prepared the (*Z*)-γ-aryloxyallyldiisopinocampheylborane from allyl *p*-methoxyphenyl ether **11**. The idea was to obtain α-aryloxy syn homoallylic alcohol, which could be readily converted to the bis-arylated anti diol, using a Mitsunobu inversion[18] with *p*-methoxy phenol as the nucleophile. Thus, the same α-phenoxy-homoallylic alcohol would afford both syn and anti diols, which could further be transformed to **2** and **1**, respectively, with a minimum number of protection/deprotection steps.

Aryloxyallylboration of benzaldehyde with *B*-γ-*p*-methoxyphenoxyallyldiisopinocampheylborane (**12**), prepared from (+)-*B*-methoxydiisopinocampheylborane and lithiated allyl *p*-methoxyphenyl ether in THF at −78 °C, followed by oxidation, provided a 76% yield of the monoprotected hydroxy olefin **13a** (Scheme 2).[19] The enantiopurity of this material was determined by HPLC analysis using a CHIRALCEL OD-H column[20] and found to be 96%.

The benzylic hydroxy group in **13a** was inverted under Mitsunobu conditions using *p*-methoxyphenol as the

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(19) (a) We believe that we have the (*S*,*S*) isomer of **13a** on the basis of analogy with similar alkoxyallylborations reported in the literature.[16] To prove that the syn homoallylic alcohol was obtained in the reaction, **13a** was inverted under Mitsunobu conditions using *p*-nitrobenzoic acid as the nucleophile followed by ester hydrolysis to obtain the (*R*,*S*)-isomer of **13a**. The specific rotation of this isomer was found to be consistent with the value reported in the literature: lit.[21a] $[\alpha]^{20}_D$ −20.6 (*c* 1.6, $CHCl_3$); observed $[\alpha]^{20}_D$ −20.5 (*c* 0.9, $CHCl_3$). (b) We also tested the aryloxyallylboration of acetaldehyde with the reagent (+)-**12** and obtained an ee of 95% as determined by HPLC.

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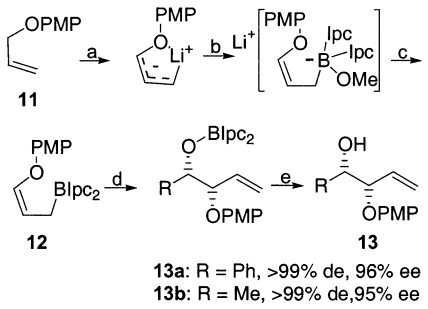
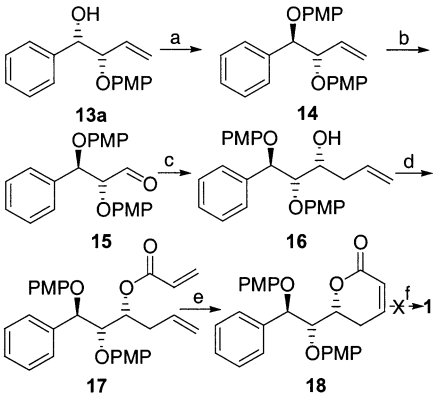
SCHEME 2[a]



[a] Reaction conditions: (a) *sec*-BuLi, THF, −78 °C, 0.5 h. (b) (+)-Ipc_2BOMe, −78 °C, 1 h. (c) $BF_3{\cdot}Et_2O$, −78 °C, 5 min. (d) RCHO, −100 °C, 10 h. (e) $NaOH/H_2O_2$, rt, 6h.

SCHEME 3[a]

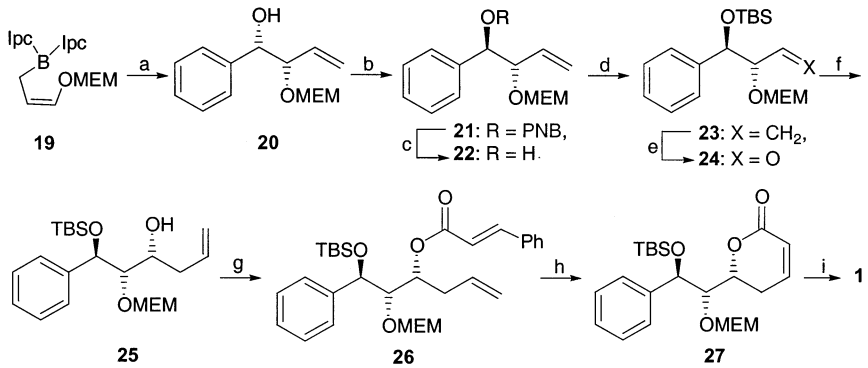


[a] Reaction conditions: (a) *p*-Methoxyphenol, PPh_3, DIAD, THF, 70 °C, 8h, 78%. (b) (i) OsO_4, NMO, acetone:water, 6 h; (ii) $NaIO_4$, acetone:water, 25 °C, 99%. (c) (i) (+)-**8a**, ether−pentane, −100 °C; (ii) NaOH, H_2O_2, rt, 6 h, 75%. (d) Acrylic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 15 h, 70%. (e) **9**, CH_2Cl_2, 60 °C, 6 h, 85%. (f) CAN, Me_2BBr, Me_3SiI, etc.

nucleophile. The reaction proceeded smoothly in refluxing THF, and we obtained a 78% yield of the inverted bis-aryloxy olefin **14**. The terminal double bond in **14** was oxidatively cleaved using $OsO_4/NaIO_4$, and allylboration of the resulting aldehyde **15** with *B*-allyldiiso-2-caranylborane[15] (**8a**) in a Et_2O−pentane mixture at −100 °C for 3 h, followed by oxidation, afforded a 75% yield of the product bis-aryloxy homoallylic alcohol **16** (Scheme 3). The diastereomeric excess was again determined using HPLC and was found to be 95%. Esterification with acrylic acid yielded the corresponding acrylate **17**, which upon ring-closing metathesis reaction with Grubbs' first generation ruthenium catalyst **9** furnished the α-pyrone **18** in 85% yield. After achieving the penultimate molecule in six steps, we proceeded to the final deprotection of the *p*-methoxyphenyl groups. Unfortunately, the usual oxidative cleavage with ceric ammonium nitrate[21] in acetonitrile provided a complex mixture of products. Varying the reaction parameters such as solvents, temperature, or stoichiometry was also futile. We also attempted the use of several other ether-cleaving agents such as dimethylbromoborane,[22] iodotrimethylsilane,[23] and *B*-bromocatecholborane.[24] However, we did not succeed in realizing the expected product in optimal yields.

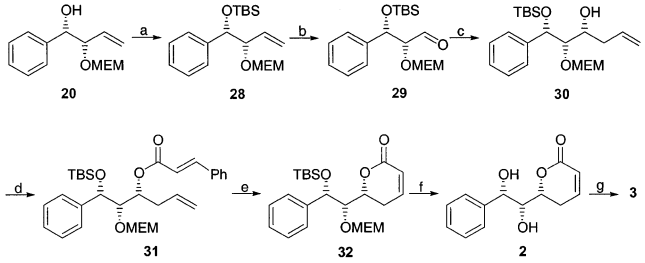
Since deprotection of the *p*-methoxyphenyl groups in our protocol proved to be difficult, we turned to protecting groups that can be cleaved under milder conditions. For this purpose, we chose the methoxyethoxymethyl (MEM) group,[25] a protective group that can be cleaved under a variety of mild Lewis and protic acid conditions. We resumed our synthesis with alkoxyallylboration of benzaldehyde with (+)-*B*-γ-methoxyethoxymethoxyallyldiisopinocampheylborane **19** (Scheme 4).[16] As expected, excellent diastereo- and enantioselectivities were achieved and the product α-alkoxyhomoallylic alcohol **20** was obtained in 71% yield and 98% ee as determined by HPLC analysis. The stereochemistry of the benzylic hydroxy group in **20** was inverted with *p*-nitrobenzoic acid under Mitsunobu conditions, and the resulting *p*-nitrobenzoate ester **21** was hydrolyzed under basic medium to obtain the monoprotected anti diol **22**. The free hydroxy group in **22** was protected as its *tert*-butyldimethylsilyl ether **23**, and the oxidative cleavage of the terminal double bond in **23**, followed by allylboration with **8a**, provided the corresponding homoallylic alcohol **25**. The diastereomeric excess was determined to be 92% by derivatizing the alcohol as its cinnamate ester[26] (**26**) and analysis using HPLC. Ring-closing metathesis of the cinnamate ester **26** with Grubbs' second-generation imidazolyl ruthenium-based catalyst **10** provided the α-pyrone **27**.[27] Both TBS and MEM groups were

SCHEME 4[a]



[a] Reaction conditions: (a) (i) PhCHO, −100 °C; (ii) $NaOH/H_2O_2$, 25 °C, 71%. (b) *p*-Nitrobenzoic acid, PPh_3, DEAD, toluene, −50 °C, 8 h, 76%. (c) NaOH, MeOH, rt, 1 h, 78%. (d) TBSCl, imidazole, DMF, 0 °C, 86%. (e) (i) OsO_4, NMO, acetone:water, 0 °C, 6h; (ii) $NaIO_4$, acetone:water, rt, 50%. (f) (i) (+)-**8a**, ether−pentane, −100 °C; (ii) NaOH, H_2O_2, rt, 6 h, 76%. (g) (*E*)-Cinnamoyl chloride, Py, DMAP, CH_2Cl_2, 0 °C, 15 h, 63%. (h) **9**, toluene, 120 °C, 3 h, 76%. (i) HCl:THF:H_2 (1:8:1) 65%.

SCHEME 5[a]



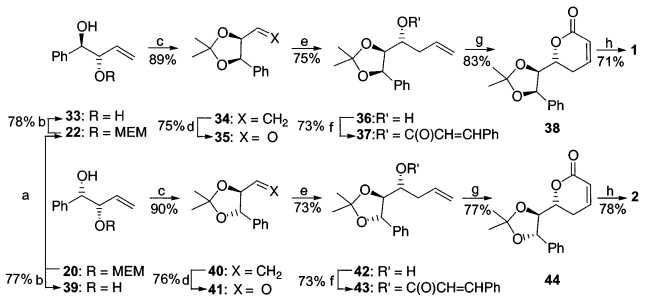
[a] Reaction conditions: (a) TBSCl, imidazole, DMF, 0 °C, 89%. (b) (i) OsO_4, NMO, acetone:water, 0 °C, 6 h; (ii) $NaIO_4$, acetone: water, 20 min, 50%. (c) (i) (+)-**8a**, ether−pentane, −100 °C, 2h; (ii) NaOH, H_2O_2, rt, 6 h, 73%. (d) (*E*)-Cinnamoyl chloride, Py, DMAP, CH_2Cl_2, 0 °C, 15 h, 70%. (e) **10**, toluene, 120 °C, 3 h, 77%. (f) HCl:THF:H_2O (1:8:1), 68%. (g) DBU, THF, 0 °C, 6 h, 86%.

deprotected in a single step with HCl in THF to afford goniodiol **1** in 65% yield. The overall yield of **1** starting from benzaldehye was 7.2%.

Starting with homoallylic alcohol **20** and essentially following the same steps mentioned above in Scheme 4, except for the Mitsunobu inversion, the synthesis of (−)-8-epigoniodiol **2** was also achieved without difficulty. The overall yield of **2** starting from benzaldehyde was 8.5%. Eventually, **2** was converted into (+)-9-deoxygoniopypyrone **3** via 1,7-diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed intramolecular Michael addition[11d] (Scheme 5). The overall yield of **3** starting from benzaldehyde was 7.2%.

In an attempt to improve the overall yield, we introduced the acetonide-protecting group in our schemes. The

SCHEME 6[a]



[a] Reaction conditions: (a) (i) *p*-Nitrobenzoic acid, PPh_3, DEAD, toluene, −50 °C; (ii) NaOH, MeOH, 25 °C. (b) Conc. HCl, MeOH, 25 °C. (c) DMP, PPTS, CH_2Cl_2. (d) (i) OsO_4, NMO, 0 °C; (ii) $NaIO_4$, 25 °C. (e) (i) (+)-**7a**, ether−pentane, −100 °C; (ii) NaOH/H_2O_2, rt. (f) (*E*)-Cinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C. (g) **10**, toluene, 120 °C. (h) HCl:THF:H_2O, rt.

required anti and syn diols **33** and **39** were prepared by the acidic cleavage of the MEM groups from **22** and **20**, respectively. Both the diols were then protected as acetonides, and the syntheses of **1** and **2** were completed via the periodate cleavage, allylboration with (+)-**7a**, DCC condensation with cinnamic acid, ring-closing metathesis, and deprotection (Scheme 6). Fortunately, the MEM-cleavage, acetonide and aldehyde formation did not require any purification, which increased the overall yields of **1** and **2** by 70% starting from benzaldehyde.

In conclusion, we have developed a simple synthesis of (+)-goniodiol, (−)-8-epigoniodiol, and (+)-9-deoxygoniopypyrone via alkoxyallylboration and ring-closing metathesis reaction pathways. We have also developed a new aryloxyallylborating agent, which furnishes PMP-protected homoallylic alcohols in high de and ee. These reaction sequences are shorter than several procedures that are currently available in the literature. All of these reactions can be carried out with ease and are amenable to scale-up. The ready availability of both isomers of inexpensive α-pinene makes these procedures especially attractive.

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(26) Esterification with acryloyl chloride provided poor yields of the acrylate. Hence, we had to resort to the cinnamate ester.

(27) Utilization of catalyst **9** provided dismal yields of **27**, and most of the starting material was recovered.