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A Metal-mediated Diastereoselective Synthesis of Precursors to the Aphid Pigment Derivatives

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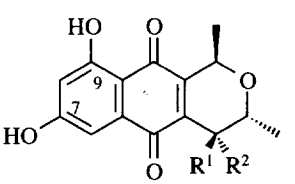
Abstract: Chiral compounds **16** and **17**, precursors to the aphid insect pigment derivatives, have been prepared in good to high yield, with complete control of the diastereoselectivity at the newly-created chiral centre C-1, through the use of metal phenolates derived from naphthol **3**.

Following our recent publication describing a novel intramolecular diastereoselective C-arylation of a chiral aldehyde by a metal phenolate in the first chiral synthesis of benzo[*c*]pyrans related to the aphid pigments,[1] we now report our complementary use of this methodology in an intermolecular process.

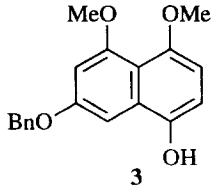
This has resulted in the synthesis of chiral precursors to the aphid pigment derivatives, Quinone A (**1**) and Quinone A' (**2**).[2] Our approach has the potential to be generally applicable to the asymmetric synthesis of many of the naphtho[2,3-*c*]pyranquinone natural products.



1 Quinone A : $R^1 = OH$, $R^2 = H$
2 Quinone A' : $R^1 = H$, $R^2 = OH$

Using simple phenols and the enantiomers of 2,3-*O*-isopropylideneglyceraldehyde, Casiraghi and co-workers found that highly diastereoselective C-arylation of chiral aldehydes can be achieved with the use of either titanium or magnesium phenolates.[3] The titanium phenolates were found to give the products of *anti* addition whereas the magnesium phenolates resulted in the *syn* addition mode. This protocol has since been successfully extended to include a variety of different chiral aldehydes.[4]

Our strategy was to apply this procedure to a suitably substituted naphthol **3**, such that C-arylation of a chiral aldehyde **4** would provide diastereoselective control of the newly-created chiral centre at C-1, thus providing compounds **5** with the appropriate chirality and functionality from which to synthesize **1** and **2**.



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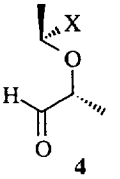

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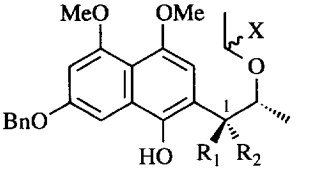
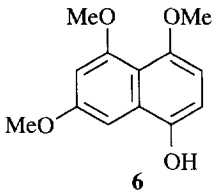


5a $R^1 = OH$, $R^2 = H$
5b $R^1 = H$, $R^2 = OH$

For model studies to establish the methodology, we chose to commence with the readily assembled naphthol **6**.[5] A logical chiral building block for the synthesis of a chiral aldehyde **4** is an ester of lactic acid and initially we used the commercially available, inexpensive (*S*)-ethyl lactate **7** for this purpose. Conversion to the 1-ethoxyethyl ether derivative **8**,[6] followed by reduction of the ester group gave predominantly the aldehyde **9**[7] (as a 55:45 mixture of diastereomers at C-1'), with some alcohol **10**, which did not affect the subsequent reactions.



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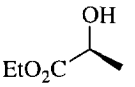

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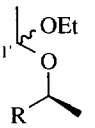
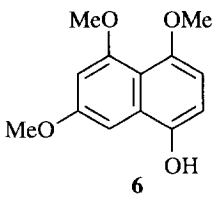


8 R = CO_2Et
9 R = CHO
10 R = CH_2OH

With some modifications to the method of Casiraghi *et al.*,[4a] the aldehyde **9** was added to a toluene solution of the triisopropoxytitanium phenolate of naphthol **6**[8] and ultrasonic irradiation was applied to the reaction mixture to improve the reactant conversion and the selectivity.[3,4a] The required product **11** was obtained as a reasonably stable oil (63% yield) and as an inseparable mixture of diastereomers at C-1" (the acetal carbon).[9] Compound **12**, diastereomeric at C-1, was not detected as a product in this reaction, leading to the conclusion that the arylation process was completely diastereoselective, affording only the product of *anti* addition **11**.

The vicinal coupling constant between 1-H and 2-H in the ^1H NMR spectrum of product **11**, being 4.3 Hz (major diastereomer) and 4.0 Hz (minor diastereomer), was diagnostic of a 1,2-*anti* arrangement of heteroatoms, *i.e.*, an *erythro* epimer, in this type of compound.[4a,10] In addition, the resonance for 1-H at δ 4.86/4.94 (major/minor) was characteristically downfield of the signal for 1-H in the C-1 epimer **12** (δ 4.57/4.56; major/minor; *vide infra*).[4a,10]



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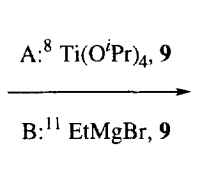
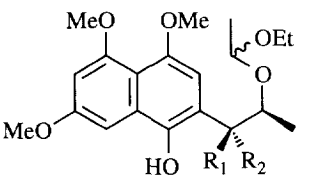




Route A: **11** R^1 = H, R^2 = OH
Route B: **12** R^1 = OH, R^2 = H

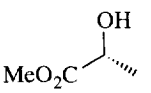
Complementary diastereoselectivity, leading to the *syn* addition product **12**, was achieved by changing the phenolate metal counterion to magnesium. This was accomplished by adding an ether solution of naphthol **6** to an aliquot of the Grignard reagent ethylmagnesium bromide in ether, replacing the ether with dry CH_2Cl_2, adding the aldehyde **9** and application of ultrasonic irradiation. Chromatography separated the two diastereomers of **12**, diastereomeric at C-1".[9] The total yield in this process was approximately 73% (the approximate ratio of recovered major and minor diastereomers was 6:4), and the absence of any of the C-1 diastereomer **11** indicated that the arylation reaction was again completely diastereoselective.

In the ^1H NMR spectra of the products **12**, the 1,2-*syn* arrangement of heteroatoms for the *threo* configuration was confirmed by the characteristically[4a,10] larger coupling constant between 1-H and 2-H of 7.8 Hz (major diastereomer) and 8.5 Hz (minor). That the signals for 1-H at δ 4.57 (major) and 4.56 (minor) were

upfield of the corresponding signals in the C-1 epimer **11** was also indicative of the *threo* series.[4a,10]

At this stage, with the success of these diastereoselective additions for model compounds, we turned our attention to molecules which would yield direct precursors to **1** and **2**. In the course of development of a racemic synthesis of the aphid pigment derivatives, such as **1** and **2**, we have examined the suitability of methyl as a protecting group at O-7 and O-9 in precursors to these naphthopyranquinones.[12] Our results indicate that methyl is a suitable protecting group for O-9, a position *peri* to a quinone carbonyl group, but that a benzyl group, which may possibly be removed with boron trichloride or alternatively by hydrogenolysis, is required at O-7.[12] Accordingly, we have developed a synthesis of the suitably substituted naphthol **3** from vanillin.[13]

The more expensive (*R*)-methyl lactate **13** was similarly converted to the aldehyde **14**, contaminated with some alcohol **15**, both as mixtures of diastereomers at C-1'.[9]



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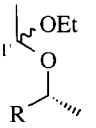
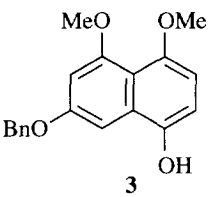


14 R = CHO
15 R = CH_2OH

Reaction of the triisopropoxytitanium phenolate of naphthol **3** with the aldehyde **14**[8] produced the required addition product **16**[9] in 43% yield.[14] Once again, it was not possible to separate the mixture of diastereomers at C-1". The exclusive formation of a single diastereomer at C-1 indicated that complete diastereoselectivity (*anti* addition mode) was achieved in the reaction.

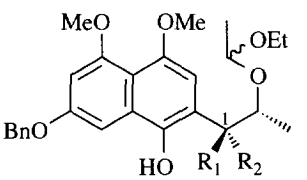
Confirmation that the arylation process had afforded the *erythro* epimer **16** was provided in the ^{1}H NMR spectrum of **16** by the magnitude of the 1-H / 2-H coupling constant of 4.1 Hz (major) and 3.7 Hz (minor), typical of a 1,2-*anti* arrangement of heteroatoms, and by the chemical shift of 1-H at δ 4.92/4.98 (major/minor), located downfield of the corresponding signals in the C-1 epimer **17**.[4a,10]



3

A:[8] $Ti(O^iPr)_4$, **14**

B:[11] EtMgBr, **14**



Route A: **16** R^1 = OH, R^2 = H
Route B: **17** R^1 = H, R^2 = OH

Preparation of the bromomagnesium phenolate of naphthol **3**, followed by addition of the aldehyde **14**,[11] produced the *syn* addition product **17**[9] (78% yield) in a completely diastereoselective process. The two diastereomeric (at C-1") components of **17** were separated by chromatography and recovered in a ratio of nearly 1:1.

The arrangement of the substituents at C-1 and C-2 in the two diastereomers of **17** was identified by the large coupling constants of 8.5 Hz (major) and 8.0 Hz (minor) between 1-H and 2-H in the ^{1}H NMR spectra of **17**, indicating a *threo* configuration. The position of the signals for 1-H at δ 4.57/4.58 (major/minor) were again upfield of the same signals in compound **16**.[4a,10]

It is important to note that the synthetic strategies developed here and in earlier work[1] may be extended to achieve the synthesis of other natural products. For example, the use of chiral malic acid esters could provide a

framework from which natural products such as some of the nanaomycins, the arizonins and medermycin may be synthesized in asymmetric form. The non-pyranoid natural product juglomycin A has recently been synthesized in chiral form with high diastereoselectivity using the reaction of a magnesium phenolate with an aldehyde derived from D-malic acid.[15]

These preliminary experiments show that compounds **16** and **17**, chiral precursors to Quinone A (**1**) and Quinone A' (**2**), can be assembled through reaction of the titanium and magnesium phenolates of naphthol **3** with the chiral (*R*)-α-alkoxyaldehyde **14**. After appropriate protection of the free hydroxy groups, it should then be possible to use a Lewis acid catalyst to achieve an intramolecular ring closure to the chiral naphthopyran system, in an analogous fashion to the acid-catalyzed Mukaiyama reaction[16] of alkyl enol ethers with acetals. The completed syntheses will be reported later.

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8. **General Procedure 1 (Route A):** Freshly prepared naphthol **6** or **3** (2.14 mmol) was dissolved in toluene (70 mL) and any water was removed as its azeotrope by distillation using a gentle flame. Neat $Ti(O^iPr)_4$ (2.51 mmol) was then added under argon and the 2-propanol/toluene azeotrope was removed by distillation. The phenolate solution was cooled in an ice bath and fresh aldehyde **9** or **14** (approx. 4.23 mmol) was added *via* syringe. After 20 min., the flask was transferred to an ultrasonic bath (Branson B3200-E4, operating at a 44–50 kHz frequency) and irradiated for 9–10 h at 10–40 °C. The mixture was diluted with ether and stirred vigorously with saturated NaF solution (1–2 days). Filtration through celite, normal work-up and column chromatography gave the products **11** or **16** as oils and as inseparable mixtures of diastereomers at C-1".
9. All new compounds prepared exhibited spectroscopic data (^1H NMR, ^{13}C NMR, IR, MS and C, H combustion analysis or HRMS) consistent with the assigned structures, except that neither a combustion analysis nor a HRMS could be completed on the high molecular weight thick oil obtained for the minor diastereomer of **17**. Optical rotations were also recorded.
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11. **General Procedure 2 (Route B):** A solution of the freshly prepared naphthol **6** or **3** (2.35 mmol) in, for **6**, dry ether (25 mL), or for **3**, dry ether (20 mL) and dry THF (10 mL), was added to an aliquot of the Grignard reagent ethylmagnesium bromide (2.94 mmol) in dry ether under argon. The solvents were removed under vacuum and dry CH_2Cl_2 (22 mL) added. The phenolate reaction mixture was cooled in an ice bath and fresh aldehyde **9** or **14** (approx. 5.30 mmol) was added. After 20 min., the flask was transferred to the ultrasonic bath and irradiated for 8 h at 10–30 °C. The reaction mixture was then poured into CH_2Cl_2 and saturated NH_4Cl solution and stirred vigorously (1–3 days). Normal work-up and column chromatography gave the products **12** or **17** with separation of the two diastereomers (at C-1"): the higher R_F diastereomer being crystalline and the lower R_F one an oil.
12. (a) Giles, R. G. F.; Green, I. R.; Niven, M. L.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2459–2467. (b) Elsworth, J. F.; Giles, R. G. F.; Green, I. R.; Ramdohr, J. E.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2469–2476.
13. The details of the synthesis of naphthol **3** and complete details, including mechanistic aspects, of the preparations of **16**, **17**, **11** and **12** will be published in a full paper.
14. To date, yield unoptimized.
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