Enantio- and Stereo-selective Route to the Taxol Side Chain *via* Asymmetric Epoxidation of *trans*-Cinnamyl Alcohol and Subsequent Epoxide Ring Opening

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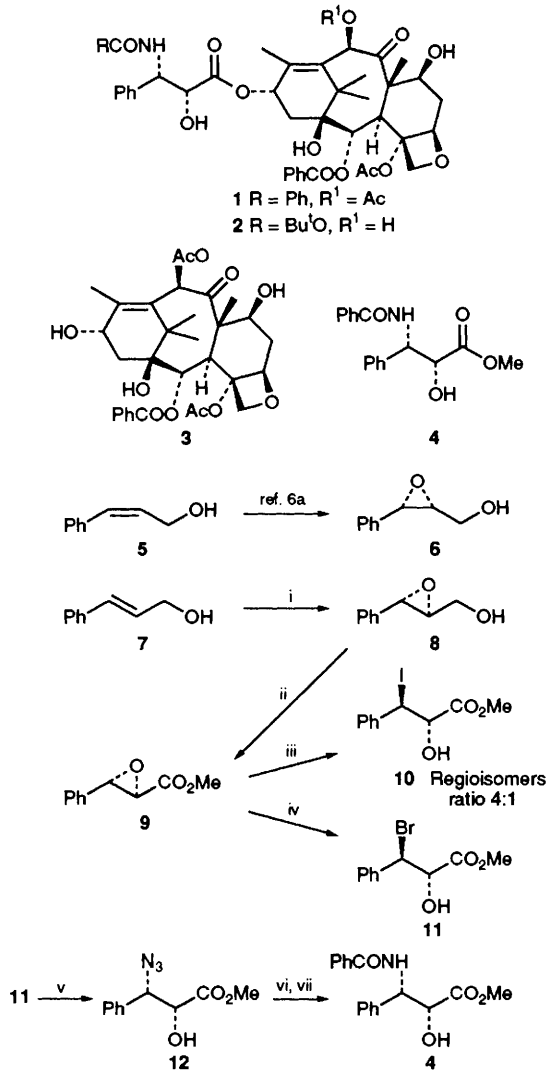
The first route to the side chain of Taxol and Taxotere, employing asymmetric epoxidation (AE) of *trans*-cinnamyl alcohol and a new highly regio- and stereo-selective opening of the epoxide ring with $MgBr_2$, is described.

Natural Taxol **1** and non-natural Taxotère **2** are probably two of the most important anticancer agents discovered.[1] Although two total syntheses of Taxol have recently been published,[2] the semisynthetic route to compounds **1** and **2** *via* the more abundant 10-deacetyl baccatin **3**[3] appears more convenient to produce large quantities of these substances.[4] Because of the importance of Taxol's C-13 side chain to the drug's activity,[5] there is still considerable interest in synthesizing compound **4** or derivatives in a highly enantio- and stereo-controlled fashion,[4,6] to be coupled with **3**. We report a novel route to **4** starting with the Sharpless AE[7] of *trans*-cinnamyl alcohol, *via* new methodology for high regio- and stereo-controlled opening of epoxy esters.



Scheme 1 *Reagents and conditions*: i, (+)-diisopropyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH, 87%; ii, $NaIO_4$, $RuCl_3$, MeCN, CCl_4, H_2O, then CH_2N_2, 56%; iii, MgI_2, Et_2O, −60 °C, 2 h, 98%; iv, $MgBr_2 \cdot Et_2O$, −60 °C to −40 °C, 6 h, 98%; v, NaN_3, Me_2CO, H_2O, 98%; vi, PhCOCl, DMAP, Et_3N, 96%; vii, H_2, Pd/C, MeOH, 88%

Surprisingly, only one published approach to the synthesis of Taxol's side chain **4** utilized the Sharpless AE for the introduction of the correct chirality:[6a] the AE was performed on *cis*-cinnamyl alcohol **5**, affording epoxyalcohol **6** (Scheme 1), with the subsequent introduction of the amino group by regioselective opening of the epoxide ring. Unfortunately, AE does not normally give good results with (*Z*)-allylic alcohol such that the epoxyalcohol **6** could not be prepared with e.e. >75–80%. The use of the commercially available (*E*)-cinnamyl alcohol **7**, on which AE can be performed with high e.e., was probably neglected because of the lack of regioselectivity in the subsequent ring opening of the epoxide.

Since recent advancements in the regioselective opening of epoxyalcohols and derivatives with metal halides[8] we decided, to start our synthesis from alcohol **7**, which was subjected to AE. The purified epoxyalcohol **8** (e.e. >96†)[9] was then oxidized with $RuCl_3/NaIO_4$[10] and methylated with CH_2N_2 to yield the known optically pure *trans*-methyl cinnamoyl ester **9**.[11]

The known utilization of MgI_2 in promoting regio- and stereo-selective opening of epoxy alcohols[12] and epoxy esters,[13] prompted us to use this methodology to obtain the iodohydrin **10**. The best results were obtained at −60 °C in diethyl ether solution with a regioselectivity of 4 : 1 in favour of the C-3 iodohydrin and with excellent chemical yield.

Since these results were not completely satisfactory we investigated the use of commercially available $MgBr_2 \cdot Et_2O$ at −60–40 °C for 6 h.‡ Only one regioisomer of the bromohydrin could be detected, giving **11**§ in quantitative yield, describing the first use of this simple metal halide reagent for regioselective opening of epoxy ester rings.¶

The synthetic sequence then followed known procedures. Quantitative introduction of N_3 with complete inversion of configuration at C-3 gave the azido alcohol **12**, which was benzoylated, without purification, with PhCOCl and finally reduced, with concomitant acyl migration,[6a] to the protected methyl ester side chain of Taxol **4**, in excellent yield.‖

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Footnotes

† Determined *via* Mosher's derivative (+)-MPTA.

‡ In a typical procedure compound **9** (3 mmol), dissolved in anhydrous diethyl ether (10 ml) in a round bottom flask under N_2, was added, at −60 °C, $MgBr_2 \cdot Et_2O$ (4.4 mol equiv.) with vigorous stirring. After 2 h the temp. was raised to −40 °C and the reaction was stopped after a further 4 h. Quenching with brine at room temp. was followed by extraction with diethyl ether and purification by column chromatography (hexanes : ether, 8 : 2) affords pure **11**.

§ A similar epoxide ring opening of compound **9** has recently been reported[6h] using the known methodology[14] used with epoxy alcohols. This procedure afforded compound **11** as a single product in 80% yield.

¶ Studies in progress demonstrate that commercially available $MgBr_2 \cdot Et_2O$ is an extremely mild and regioselective reagent for epoxide ring opening of 2,3-epoxy alcohols, esters and derivatives to the corresponding 3-bromohydrins.

‖ Compound **4** $[\alpha]_D^{20} = -47.7$ ($c = 1.2$ in MeOH); lit.[6c] $[\alpha]_D = -48$ ($c = 1.0$ in MeOH); lit.[6h] $[\alpha]_D = -49$, ($c = 1.0$ in MeOH); lit.[6i] $[\alpha]_D = -46.8$ ($c = 1.0$ in MeOH). Satisfactory spectroscopic data were obtained for compounds **11**, **12** and **4**.

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