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A Concise Synthesis of Enantiomerically Pure Taxane C-Ring *via* the [2,3] Wittig Rearrangement

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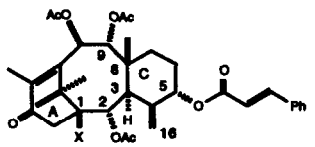
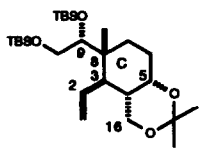
Abstract: An efficient, stereoselective synthesis of an enantiomerically pure C-ring precursor **14-S** of O-cinnamoyltaxicins-I and -II has been achieved from 3-methyl-2-cyclohexen-1-ol, using a [2,3] Wittig rearrangement as the key step.

We have recently demonstrated the utility of the Ni(II)/Cr(II)-mediated coupling reaction for construction of the taxane ring system.[1] In this communication, we would like to report the efficient synthesis of an enantiomerically pure C-ring precursor **14-S** of O-cinnamoyltaxicins-I and -II.[2]

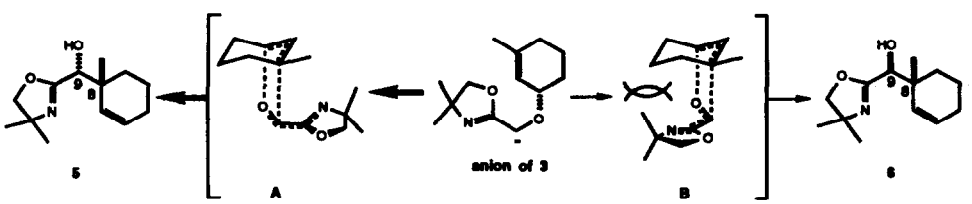


O-Cinnamoyltaxicin-I Triacetate (X=OH)
O-Cinnamoyltaxicin-II Triacetate (X=H)



14-S

The utility of the [2,3] Wittig rearrangement in the stereocontrolled construction of carbon-carbon bonds has been well documented.[3] We were hopeful that such a rearrangement, cf. **3**→**5**, could be used to: a) generate the desired C.9 alcohol stereochemistry, b) stereoselectively install the C.8 quaternary carbon, and c) provide a suitable handle for functionalization at C.3, C.4 and C.5.[4] Two possible transition states for the proposed [2,3] Wittig rearrangement are depicted in Scheme 1. Transition state **B**, leading to the undesired alcohol **6**, contains an unfavorable steric interaction between the carbocycle and the methyl group of the oxazoline. Conversely,

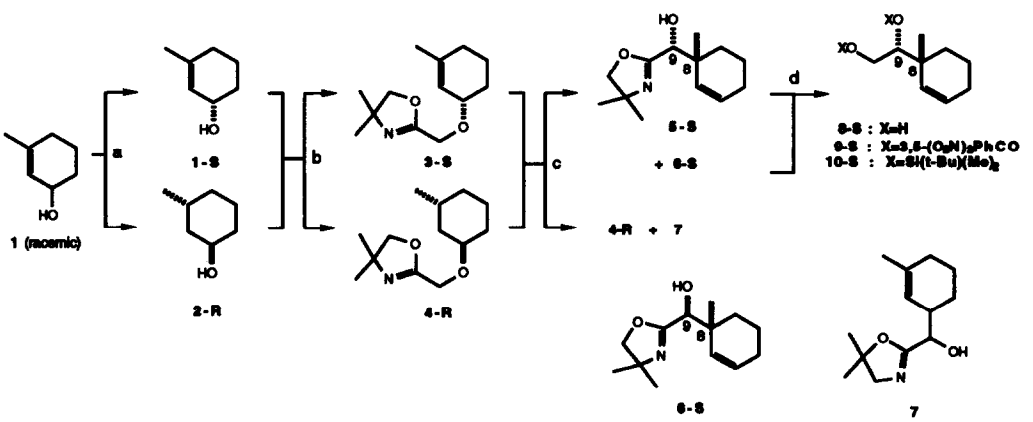


Scheme 1

transition state **A** lacks such a destabilizing steric interaction, resulting in the desired stereochemistry at C.9.[5] Obviously, optically active (*S*)-3-methyl-2-cyclohexen-1-ol should yield a precursor of the C-ring with the desired absolute configuration at C.8 and C.9.

Thus, racemic 3-methyl-2-cyclohexen-1-ol (**1**) was kinetically resolved according to Noyori's procedure to provide a mixture of (*S*)-3-methyl-2-cyclohexen-1-ol (**1-S**) and (*1R,3R*)-3-methylcyclohexan-1-ol (**2-R**).[6,7] This mixture was slightly contaminated with (*R*)-3-methyl-2-cyclohexen-1-ol and (*1S,3S*)-3-methylcyclohexan-1-ol (Scheme 2).[8] Treatment of this mixture with potassium hydride and 2-chloromethyloxazoline[9] afforded a mixture of the methyloxazoline-ethers **3-S** and **4-R**, along with trace amounts of their respective enantiomers.

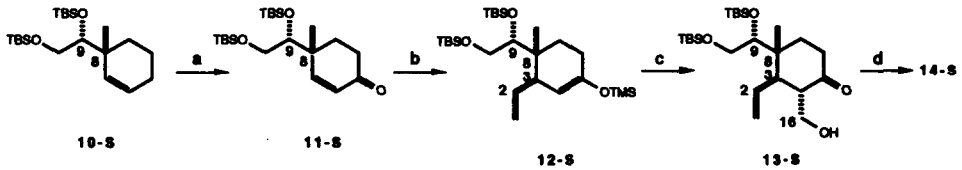
The [2,3] Wittig rearrangement of cyclic allylic ethers has been reported to be accompanied with substantial amounts of products arising from [1,2] rearrangement, cf. **3-S**→**7**.[3] Indeed, when the reaction temperature was elevated to 0 °C during the first hour of reaction time, this side-reaction was observed to the extent of a 4:1 ratio of [2,3]:[1,2] rearrangement products. However, an 8-10:1 ratio of [2,3]:[1,2] rearrangement products was observed when the reaction temperature was maintained at -78 °C.[10,11] The diastereoselectivity, i.e. **5-S**:**6-S**, for the [2,3] Wittig rearrangement was 12:1, as determined by ^{1}H NMR. It is worthwhile to note that after this rearrangement **4-R** (recovered largely unchanged[12]) and **7**, as well as a minor amount of their respective enantiomers, were removed by silica gel chromatography. Unfortunately, we were unable to separate **6-S** from **5-S** at this point. Conversion of the oxazolines **5-S** and **6-S** to their iminium salts, followed by base hydrolysis,[13] furnished the corresponding α-hydroxy acids. The yields associated with hydride-reduction of these acids under a variety of conditions were uniformly poor; therefore the α-hydroxy acids were first converted into the corresponding α-hydroxy methyl esters, which were then cleanly reduced to the corresponding diols.



Scheme 2. Reagents and Reaction conditions. a. H_2, Noyori's catalysis, MeOH. b. KH, DME, 2-chloromethyloxazoline. c. *n*-BuLi, THF, followed by silica gel column chromatography. d. 1. MeI, DMSO. 2. KOH, H_2O. 3. MeOH, *p*-TsOH. 4. LAH, Et_2O. 5. 3,5-$(NO_2)_2C_6H_3COCl$, pyr, DMAP, followed by fractional recrystallization. 6. MeOH, NaOH, H_2O. 7. TBSOTf, 2,6-lutidine, CH_2Cl_2.

In order to obtain enantiomerically pure **8-S**, it was necessary to remove approximately 8% of the undesired C.9-diastereomeric diol and its enantiomer as well as to increase the enantiomeric excess of **8-S** from its current value of 90%. Derivatization of impure **8-S** to the bis-3,5-dinitrobenzoate, followed by two fractional recrystallizations, afforded enantiomerically pure **9-S** (mp 159-160 °C). Base-hydrolysis of this bis-benzoate, gave enantiomerically pure diol **8-S** ($[\alpha]_D$ -45° (*c* 1.3, $CHCl_3$)) in 66% overall yield from impure **8-S**. ^1H and ^{19}F NMR analysis of the C.10 Mosher ester of **8-S** confirmed it to be pure. Conversion of **8-S** to the bis(*tert*-butyldimethylsilyl)ether **10-S** was achieved under the standard conditions.

With enantiomerically pure material in hand, we continued functionalization of the C-ring (Scheme 3).[14] Allylic oxidation of **10-S** by PDC/*tert*-butyl hydroperoxide[15] furnished the enone **11-S** in 78% yield (90% yield based on recovered starting material). Addition of **11-S** to a THF solution of higher order vinyl cuprate,[16] followed by TMSCl quench, afforded **12-S** in a 16:1 diastereoselectivity. Incorporation of the C.16 carbon was originally planned *via* trapping of formaldehyde or its synthetic equivalent with the enolate resulting from the conjugate addition. However, several attempts provided irreproducible results. This difficulty was overcome by using the ene-type chemistry recently developed by Yamamoto. Addition of **12-S** to a solution of 1,3,5-trioxane in the presence of the Yamamoto MAPH reagent,[17] followed by acid hydrolysis, cleanly gave the β-hydroxy ketone **13-S** in 60% yield from **11-S**. Selectride reduction of **13-S**, followed by acetonide formation, furnished the C-ring precursor **14-S** ($[\alpha]_D$ -6.4° (*c* 1.3, $CHCl_3$))[18] in 60% yield. The structure of **14-S** was established on comparison with a racemic sample prepared *via* a different route.[14]



Scheme 3. Reagents and Reaction conditions. a. PDC, Celite, *t*-BuOOH, PhH. b. $(CH_2{=}CH)_2Cu(CN)Li_2$, THF, followed by TMSCl/Et_3N. c. 1. MAPH, 1,3,5-trioxane, CH_2Cl_2. 2. HCl, H_2O. d. 1. LS-Selectride, Et_2O, followed by H_2O_2/aq. NaOH work-up. 2. 2,2-$(CH_3O)_2CH(CH_3)_2$, *p*-TsOH.

In summary, the enantiomerically pure C-ring precursor **14-S** of taxicins-I and -II was synthesized in 14 steps from (*S*)-3-methyl-2-cyclohexen-1-ol (90% ee). This synthesis was routinely carried out on a scale of 25-50 grams of **1-S**. Efforts for conversion of **14-S** to O-cinnamoyltaxicins-I and -II are in progress in this laboratory.

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3. For a review, see: Nakai, T.; Mikami, K. *Chem. Reviews*, **1986**, *86*, 885. For some examples related to the present work, see: Rossano, L. T.; Plata, D. J.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 5189.

4. The numbering in this paper corresponds to that adopted in the taxane class of natural products.[2]

5. The [3,3] rearrangement of glycolate esters derived from 3-methyl-2-cyclohexen-1-ol was also studied. The rearrangement of 3-methyl-2-cyclohexenyl (2-benzyloxy)ethanoate afforded the undesired C.9 stereochemistry (α-OH:β-OH=1:5). For the [3,3] rearrangement of glycolate esters, see: Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103 and references cited therein.

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7. We gratefully thank Dr. Hawkins at Eisai Research Institute for preparation of the Noyori catalyst and subsequent reduction. The reduction was carried out in 82 gram scale (0.73 mole) in the presence of 0.2% mole of the catalyst.

8. The optical purity of an analytical sample of this mixture was determined to be ca. 90% ee by ^{1}H NMR of its Mosher ester.

9. We gratefully thank Professor Kallmerten at Syracuse University for details of the preparation of 2-chloromethyloxazoline.

10. The temperature dependence of [2,3] *versus* [1,2] rearrangement for cyclic allylic ethers has been previously noted.[3]

11. The [1,2] rearrangement product **7** obtained at -78 °C was a single diastereomer.

12. A very minor product, probably derived from **4-R**, was isolated.

13. Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.

14. The transformation of **10** to **14** was originally studied in this laboratory by using racemic **10** obtained by an alternative route. The structure of **14** in the racemic series was established by an X-ray analysis of C.10 *p*-bromobenzoate: W. H. Miller, M. H. Kress, R. Ruel, and Y. Kishi, unpublished results.

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18. ^{1}H NMR of **14-S** ($CDCl_3$; 500 MHz): δ 5.47 ppm (1H, dt, *J*=17.0, 10.0 Hz), 5.19 (1H, dd, *J*=11.0, 2.0), 5.10 (1H, dd, *J*=17.0, 2.0), 4.13 (1H, d, *J*=2.0), 3.98 (1H, dd, *J*=15.0, 8.0), 3.87 (1H, dd, *J*=12.0, 3.0), 3.79 (1H, d, *J*=12.0), 3.51 (2H, m), 2.86 (1H, dd, *J*= 10.5, 10.0), 1.63 (3H, m), 1.44 (3H, s), 1.39 (3H, s), 1.31 (1H, m), 1.24 (1H, d, *J*=12.0), 0.92 (3H, s), 0.90 (9H, s), 0.89 (9H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s).

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