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AN ENANTIOSELECTIVE APPROACH TO RING A OF TAXOL USING THE WIELAND-MIESCHER KETONE

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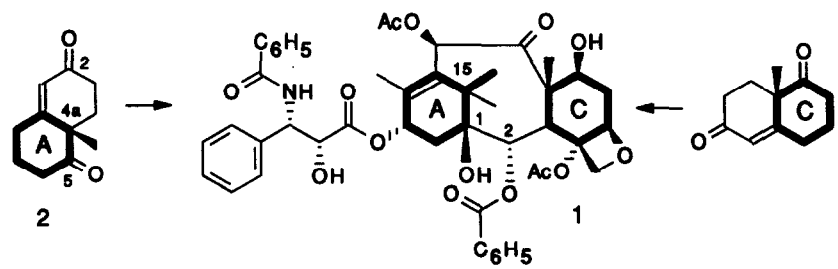
Abstract. The selective protection of the S-(+)-enantiomer of the Wieland Miescher ketone (2) as the tert-butyldimethylsilyl-protected cyanohydrin 7 and the oxidative cleavage of an α-ketol 8 that was derived from 7 provided a model 10 for the A ring of the taxol (1) possessing the correct C-1 stereochemistry of taxol and functionality suitable for further elaboration.

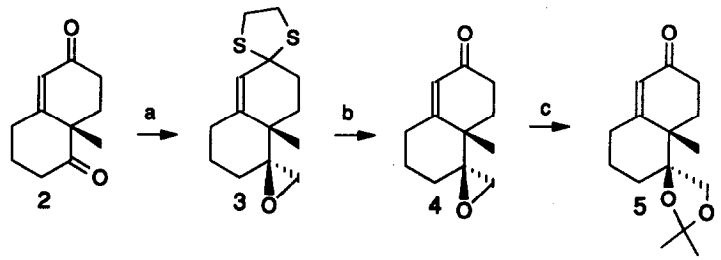
The need to devise a synthesis[1] of taxol (1) in homochiral form and the presence of two "masked" *cis*-2-methylcyclohexanol subunits (emboldened lines in structure below) suggested that the A and C rings of taxol could be derived from the S-(+)-enantiomer of the Wieland-Miescher ketone (2). Several studies[2] recognized the Wieland-Miescher ketone as a potential source of the *cis*-2-methyl-cyclohexanol subunit of ring C. In our retroanalysis, *both* the A and C rings derived from the S-(+)-enantiomer of the Wieland-Miescher ketone (2), and we report a synthesis of a model for the A ring of 1 that addresses the problem of introducing the C-1 stereocenter in 1 with correct absolute stereochemistry at the outset of the synthesis.



The Hajos-Parrish procedure[3] using L-proline provided the S-(+)-enantiomer of the Wieland-Miescher ketone (2) in high enantiomeric purity (99%). The addition of a "hydroxymethyl" nucleophile, such as sodium dimethylsulfoxonium methide,[4] the Grignard reagent of dimethylisopropoxysilylmethyl chloride[5] or trialkylsilyl cyanides,[6] to the C-5 carbonyl group of 2 without protection of the conjugated carbonyl group at C-2 failed to exhibit the desired level of selectivity. As shown in Scheme 1, the

protection of the C-2 carbonyl group as the dithioketal **3**, and the addition of sodium dialkylsulfoxonium methide delivered the desired spiroepoxide **3** in 87% yield. However, the further conversion of the spiroepoxide **4** to the spiroketal **5**, proceeded in only modest yield.

Scheme 1.

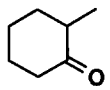
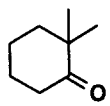
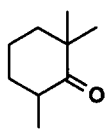
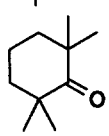


a, (1) $HSCH_2CH_2SH$, p-TsOH, HOAc (90%); (2), $[Me_2S(O)=CH_2]Na$ (87%); b, $Tl(NO_3)_2$, aq. MeOH, THF (65%); c, $TiCl_4$, acetone, $CH_3C(OCH_3)=CH_2$ or $BF_3.Et_2O$, acetone (15-30%).

The limited success of the approaches designed to add a "hydroxymethyl" nucleophile to **2** led to the utilization of a trialkylsilyl-protected cyanohydrin because it offered the best combination of stability toward various reagents needed elsewhere in the route and convertibility to the C-1 α-hydroxyaldehyde that we will require. As shown in Scheme 2, protection of **2** as the dithioketal and the addition of tert-butyldimethylsilyl cyanide (TBDMSCN) led to the protected cyanohydrin **6** in 86% yield in which the ratio of the desired C-1 epimer **6** to the undesired epimer was 10.1 to 1. Although there are a few reports of the addition of tert-butyldimethylsilyl cyanide to hindered ketones[6] the zinc iodide-catalyzed addition of this reagent as well as the addition of a new reagent, tert-butyldiphenylsilyl cyanide,[7] to substituted cyclohexanones proceeded in good yield (Table 1). The stereochemical issue with respect to the C-1 center in the principal diastereomer **6** was settled unambiguously by X-ray crystallography. Deprotection of **6** with thallium nitrate furnished the protected Wieland-Miescher ketone **7** in high yield.

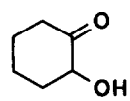
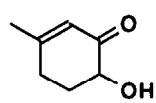
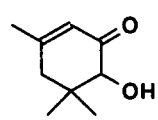
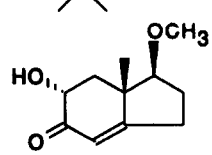
In order to rupture the bicyclic ring system of the Wieland-Miescher ketone, we investigated the cleavage of unsaturated α-ketols (Table 2). As shown in Table 2, periodate[8] was the most effective reagent of those examined for the cleavage of unsaturated α-ketols. A $Pb(OAc)_4$ oxidation[9] of **7** furnished the α'-acetoxyenone and saponification provided the unsaturated α-ketol **8**. Cleavage of **8** and treatment with diazomethane afforded the aldehyde **9**, and decarbonylation[10] with Wilkinson's reagent afforded the desired α,β-unsaturated ester **10**. In summary, the Wieland-Miescher ketone **2** may provide a suitable

Table 1. The Addition of TBDMSCN and TBDPSCN to Substituted Cyclohexanones.

Cyclohexanone	TBDMS-cyanohydrin yield (conditions)	TBDPS-cyanohydrin yield (conditions)
		92% (B, 8h, 1.5 eq)
	94% (A, 2h, 1.3 eq)	no reaction (A, 14h, 1.5 eq) 92% (B, 8h, 1.5 eq)
	83% (A, 20h, 1.3 eq)	no reaction (A, 24h, 2 eq)
	92% (A, 4d, 1.5 eq)	85% (B, 6d, 2 eq)

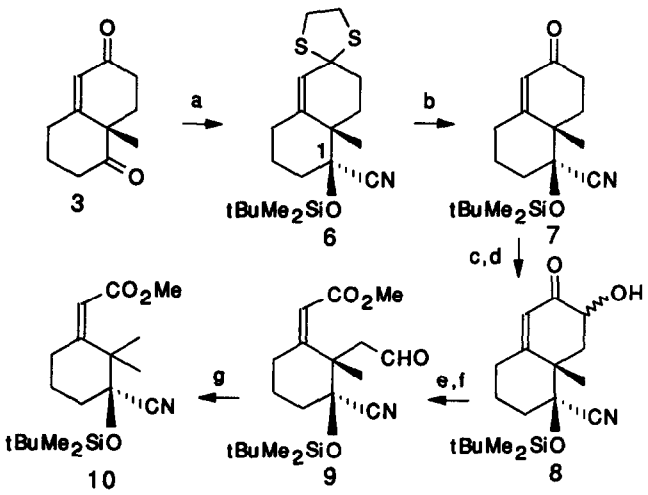
Procedure A: TBDMSCN or TBDPSCN (equiv), ZnI_2 (*ca.* 0.03 equiv), CH_2Cl_2, 25°C;
Procedure B: TBDMSCN or TBDPSCN (equiv), ZnI_2 (0.23 equiv), CH_2Cl_2, 25°C.

Table 2. Cleavage Reactions of Saturated and Unsaturated α-Ketols.

α-Ketol	$NaIO_4$	$NaBiO_3$	$Pb(OAc)_4$	MnO_2
	81%	72%	5%	0%
	84%	0%	0%	--
	70%	20%	60%	--
	60%	0%	10%	--

platform from which to elaborate the A ring of taxol (1) and progress toward the introduction of the remaining A ring functionality and the elaboration of the B ring will be reported in due course.

Scheme 2.



a, (1) $HSCH_2CH_2SH$, p-TsOH, HOAc, 25°C, (2), TBSCN, ZnI_2, CH_2Cl_2 (86% overall); b, $Tl(NO_3)_2$, aq. MeOH, $CHCl_3$, THF (90%); c, $Pb(OAc)_4$ (3 equiv), benzene, 68 h, reflux (85%) d, K_2CO_3 (0.13 equiv), MeOH (85%); e, $NaIO_4$, aq. t-BuOH; f, CH_2N_2 (75% overall for e, f); g, $RhCl(PPh_3)_3$ (1 equiv), C_6H_6, 80°C (70%).

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