Chiral synthesis of the CD ring unit of paclitaxel from D-glucal

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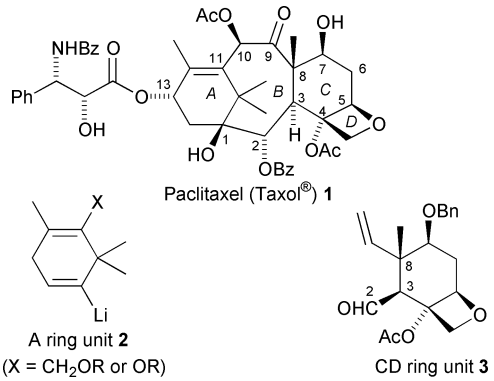
The chiral synthesis of the fully functionalized CD ring unit of paclitaxel 3 is described; the three component coupling reaction of a cyclohexenone derived from D-glucal by way of Ferrier's carbocyclization with vinyl cuprate and formaldehyde effectively constructed the carbon framework of 3.

Paclitaxel (Taxol®) **1** is a well-documented natural diterpenoid and is known to show highly promising antitumor activity.[1] The challenging structure as well as important biological activities of **1** has attracted much attention of the synthetic community, and six successful total syntheses of **1** have been reported to date.[2] Our own synthetic endeavor to paclitaxel required the fully functionalized CD ring unit **3** as the key intermediate; the formyl function at C-3 (paclitaxel numbering) would be utilized for the coupling reaction with a paclitaxel A-ring **2**, and the vinyl group at C-8 would serve as the key functionality for the construction of a taxane skeleton. Successful precedents for preparation of taxane tricarbocyclic structures by way of final B-ring closure of connected AC ring systems revealed the possibility of this approach.[3] The highly oxygenated structure of **3**, which contains five contiguous chiral centers including a quaternary carbon and a strained oxetane ring is synthetically fascinating, and it is a significant aim to establish an effective synthetic route to **3** from readily available material for the development of a novel approach to the clinically important compounds.[4] In this communication, we report a synthesis of **3**, which utilized commercially available tri-*O*-acetyl-D-glucal **4** as a chiral starting material.



The known methyl glycoside **5**,[5]† derived from **4** in a two step reaction (90% overall yield) (Scheme 1) was converted into primary iodide **6**† in 87% yield, which was then treated with NaH and benzyl bromide to afford enopyranoside **7**† in 80% yield. Ferrier's carbocyclization[6] of **7** using a catalytic amount of $Hg(OCOCF_3)_2$,[7] followed by β-elimination cleanly generated cyclohexenone **8** (80% yield). Reaction of **8** with MeLi gave 1,2-adduct **9**, whose oxidation with PCC afforded **10** in 83% yield from **8**.

With a chiral cyclohexenone **10** in hand, generation of the quaternary carbon at C-8 and the C–C bond at C-3 by a three component coupling reaction[8]‡ of **10**, a vinyl metal species, and formaldehyde in a one-pot reaction was investigated. Treatment of **10** with higher order vinylcuprate [$(vinyl)_2$-$CuCNLi_2$] in Et_2O at −78 °C caused the stereoselective conjugated addition of the vinyl group to give an enolate intermediate,§ which was then reacted with a THF solution of formaldehyde at −60 °C to provide **11** {mp 50–52 °C; $[\alpha]_D^{23}$ + 12 (*c* 1.0, $CHCl_3$)} and its C-3 isomer **12** {$[\alpha]_D^{23}$ + 93 (*c* 1.0, $CHCl_3$)} in 62 and 33% isolated yields, respectively. The observed coupling constants and NOE unambiguously supported the structure of **11** (Scheme 2). Base-induced epimerization of **12** gave an additional amount of **11** (44% yield, **12** was recovered in 51% yield); thus **11** was obtained in 76% overall yield from **10** after one-cycle epimerization of **12**. Protection of the hydroxy group in **11** as a THP ether afforded **14** in 90% yield. To introduce an hydroxy function at C-5, ketone **14** was treated with LiHMDS at −78 °C, and the resulting kinetic enolate was trapped with TMSCl to provide silylenol ether, which was then reacted with MCPBA at −20 °C followed by treatment with TMSCl and triethylamine to give **15** and **16** in 53 and 26% isolated yields, respectively. Reaction of **15** with Tebbe's reagent[9] and subsequent removal of the silyl protecting group under basic conditions afforded *exo*-alkene **17** in 64% yield.¶ Vanadium catalyzed epoxidation[10] of **17** gave **18** as a single isomer in 81% yield. Reaction of **18** with potassium acetate in DMF, followed by treatment with acetic anhydride and pyridine at rt gave **19** in 95% yield. The secondary hydroxy group in **19** was mesylated to afford **20** (96% yield). Removal of the *O*-acetyl group, followed by reaction with DBU[4c] in toluene at 100 °C cleanly generated oxetane **21** in 65% yield. Acetylation of tertiary alcohol in **21** afforded **22** (100%). Deprotection of the *O*-THP group in **22** with CAN[11]‖ gave **23**, which was oxidized with TPAP[12] to furnish the desired aldehyde **3** {$[\alpha]_D^{23}$ −137 (*c* 0.07, $CHCl_3$)} in 80% yield from **22**. The observed NOE between the methyl at C-8 and the formyl hydrogen, H-20, and H-6_β, and between H-7 and H-3 clearly supported the assigned structure.

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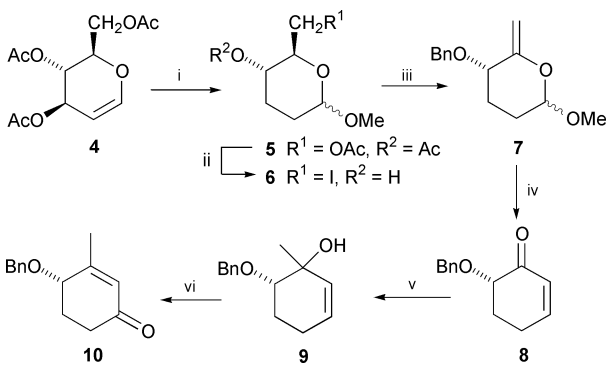
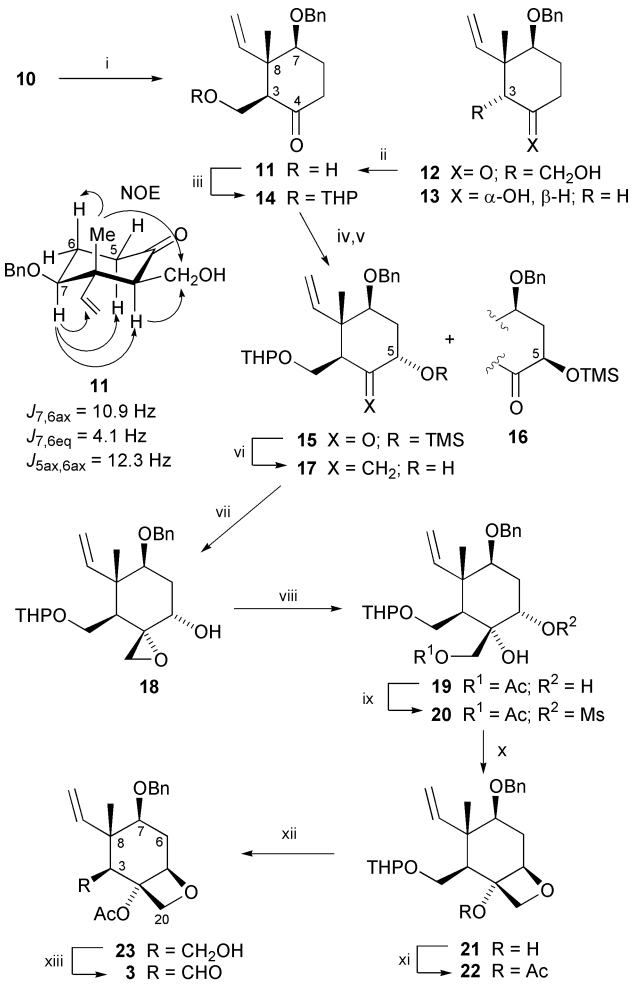


Scheme 1 Bn = $-CH_2Ph$. *Reagents and conditions*: i, MeOH, $BF_3{\cdot}OEt_2$, PhH, 0 °C, then H_2, 10% Pd-C, EtOAc, rt; ii, MeONa, MeOH, 0 °C, then I_2, Ph_3P, imidazole, THF, rt; iii, NaH, DMF, 0 °C, then BnBr, *n*-Bu_4NI, DMF, 0 °C; iv, $Hg(OCOCF_3)_2$ (5 mol%), acetone–H_2O (2:1), 0 °C, then MsCl, Et_3N, CH_2Cl_2, 0 °C; v, MeLi, Et_2O, −78 °C; vi, PCC, molecular sieves 4 Å (powder), CH_2Cl_2, rt.



Scheme 2 THP = tetrahydropyran-2-yl, TBS = $-SiMe_2(t\text{-Bu})$, Ms = $-SO_2Me$. *Reagents and conditions*: i, CuCN (2 eq.), vinyllithium (4 eq.), Et_2O, −78 °C, 10 min, then formaldyhyde in THF (1 mol l^{-1}, excess amount), −60 °C, 15 min; ii, K_2CO_3, MeOH, rt; iii, 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, rt; iv, LiHDMS, THF, −78 °C, then TMSCl–Et_3N (1 : 1, v/v), −78 °C; v, MCPBA , −20 °C, CH_2Cl_2, then TMSCl, Et_3N, CH_2Cl_2; vi, Tebbe reagent, THF, rt, then K_2CO_3, MeOH, rt.; vii, *t*-BuOOH, $VO(acac)_2$, rt; viii, AcOK, 18-crown-6, DMF, 100 °C, then acetic anhydride, pyridine, rt; ix, MsCl, DMAP, CH_2Cl_2, rt; x, K_2CO_3, MeOH, rt; then DBU, toluene, 100 °C; xi, acetic anhydride, DMAP, pyridine, 40 °C; xii, CAN (3 mol%), CH_3CN–borate buffer (pH 8, 1 : 1), 50 °C; xiii, TPAP, NMO, rt.

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Notes and references

† This compound was an anomeric mixture (α : β = *ca.* 4 : 1), and used in the next reaction without separation.

‡ A similar approach (starting from D-glucose) has been reported by Ermolenko, see ref 4*d*.

§ Conjugated addition of the vinyl group to enone **10** was found to proceed highly stereoselectively. When the intermediate enolate was treated with aqueous NH_4Cl, a 1,4-adduct was obtained as a single isomer in 95% yield. Reduction of the 1,4-adduct with $NaBH_4$ afforded a cyclohexanol derivative **13**, which was acylated with (*R*)- and (*S*)-acetylmandelic acid (DCC, DMAP) to give (*R*)- and (*S*)-acetylmandelate derivatives, respectively. ^1H NMR analyses of the acetylmandelates revealed that they showed quite different spectra, and no signal due to the (*R*)-isomer was observed in the spectrum of the (*S*)-isomer, indicating the cyclohexanol **13** possessed high optical purity (~100% ee), and no racemization had occurred during the preparation of **8** and **10** and the 1,4-addition process.

¶ When compound **16** was subjected to the same reaction conditions, no reaction took place resulting in the recovery of **16**.

‖ Under the conditions of deprotection of the *O*-THP group with PPTS in EtOH, the primary hydroxy group in the resulting **23** further attacked the oxetane ring to generate a significant amount of a THF derivative.

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