

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

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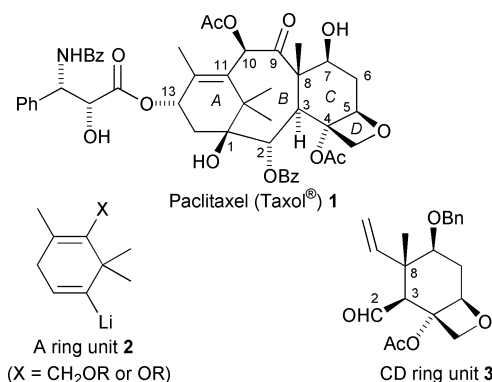
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The chiral synthesis of the fully functionalized CD ring unit of paclitaxel **3** is described; the three component coupling reaction of a cyclohexenone derived from D-glucal by way of Ferrier's carbocyclization with vinyl cuprate and formaldehyde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



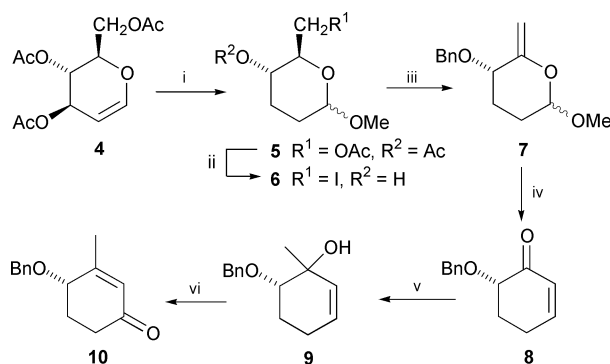
date.² Our own synthetic endeavor to paclitaxel required the fully functionalized CD ring unit **3** as the key intermediate; the formyl function at C-3 (paclitaxel numbering) would be utilized for the coupling reaction with a paclitaxel A-ring **2**, and the vinyl group at C-8 would serve as the key functionality for the construction of a taxane skeleton. Successful precedents for preparation of taxane tricyclic 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 carbocyclization⁶ of **7** using a catalytic amount of Hg(OCOCF₃)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**.

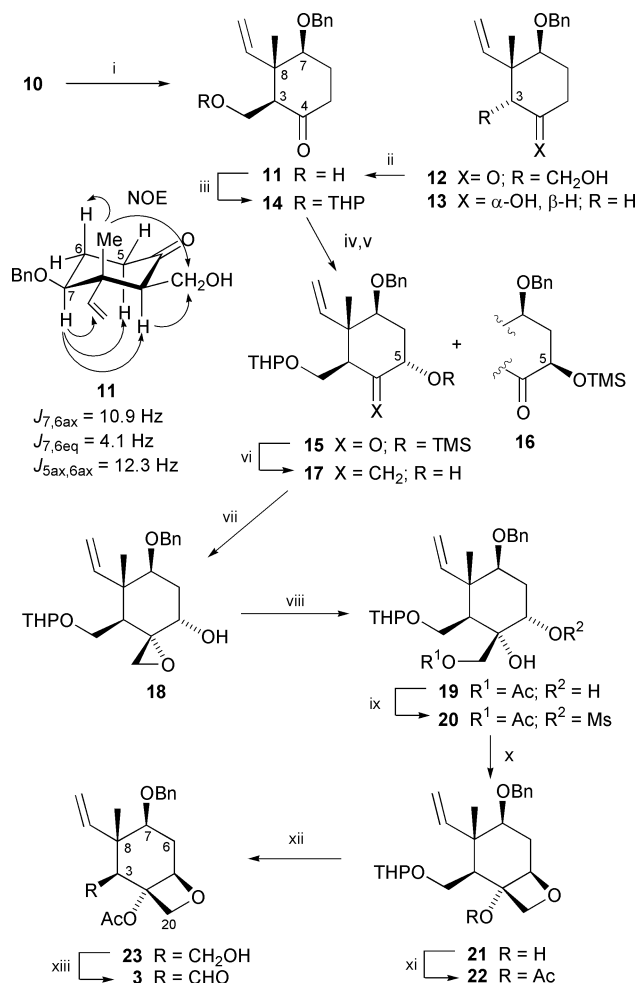
With a chiral cyclohexenone **10** in hand, generation of the quaternary carbon at C-8 and the C–C bond at C-3 by a three component coupling reaction^{8†} of **10**, a vinyl metal species, and formaldehyde in a one-pot reaction was investigated. Treatment of **10** with higher order vinylcuprate [(vinyl)₂-

CuCNLi₂] in Et₂O 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; [α]_D²³ + 12 (c 1.0, CHCl₃)} and its C-3 isomer **12** {[α]_D²³ + 93 (c 1.0, CHCl₃)} 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 a 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 reagent⁹ and subsequent removal of the silyl protecting group under basic conditions afforded *exo*-alkene **17** in 64% yield.[¶] Vanadium catalyzed epoxidation¹⁰ 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 TPAP¹² to furnish the desired aldehyde **3** {[α]_D²³ – 137 (c 0.07, CHCl₃)} 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 = –CH₂Ph. Reagents and conditions: i, MeOH, BF₃·OEt₂, PhH, 0 °C, then H₂, 10% Pd-C, EtOAc, rt; ii, MeONa, MeOH, 0 °C, then I₂, Ph₃P, imidazole, THF, rt; iii, NaH, DMF, 0 °C, then BnBr, *n*-Bu₄NI, DMF, 0 °C; iv, Hg(OCOCF₃)₂ (5 mol%), acetone–H₂O (2:1), 0 °C, then MsCl, Et₃N, CH₂Cl₂, 0 °C; v, MeLi, Et₂O, –78 °C; vi, PCC, molecular sieves 4 Å (powder), CH₂Cl₂, rt.



Scheme 2 THP = tetrahydropyran-2-yl, TBS = $-\text{SiMe}_2(t\text{-Bu})$, Ms = $-\text{SO}_2\text{Me}$. **Reagents and conditions:** i, CuCN (2 eq.), vinyl lithium (4 eq.), Et₂O, -78°C , 10 min, then formaldehyde in THF (1 mol l⁻¹, excess amount), -60°C , 15 min; ii, K₂CO₃, MeOH, rt; iii, 3,4-dihydro-2H-pyran, PPTS, CH₂Cl₂, rt; iv, LiHDMS, THF, -78°C , then TMSCl-Et₃N (1:1, v/v), -78°C ; v, MCPBA, -20°C , CH₂Cl₂, then TMSCl, Et₃N, CH₂Cl₂; vi, Tebbe reagent, THF, rt, then K₂CO₃, 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, CH₂Cl₂, rt; x, K₂CO₃, MeOH, rt; then DBU, toluene, 100°C ; xi, acetic anhydride, DMAP, pyridine, 40°C ; xii, CAN (3 mol%), CH₃CN–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 ($\alpha:\beta = ca. 4:1$), and used in the next reaction without separation.

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

§ Conjugated addition of the vinyl group to enone **10** was found to proceed highly stereoselectively. When the intermediate enolate was treated with aqueous NH₄Cl, a 1,4-adduct was obtained as a single isomer in 95% yield. Reduction of the 1,4-adduct with NaBH₄ 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 ($\sim 100\%$ 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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