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Synthesis of the CD ring system of paclitaxel by atom-transfer radical annulation reaction

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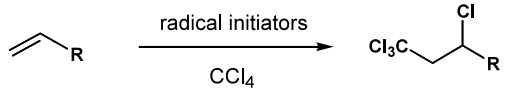
Abstract—Atom-transfer radical annulation of diene derived from D-glucose under Kharasch conditions provided access to the fully functionalized CD ring system of paclitaxel.

The atom-transfer radical reaction has been found quite useful for functionalizing unsaturated organic molecules.[1] The Kharasch reaction, which involves the addition of various halocarbons to olefins in the presence of radical initiators, is particularly effective for this purpose (Scheme 1).[2–4] Poly-halogenated compounds obtained by this reaction have been used as versatile intermediates for organic synthesis owing to their compatibility with numerous transformations.[5]

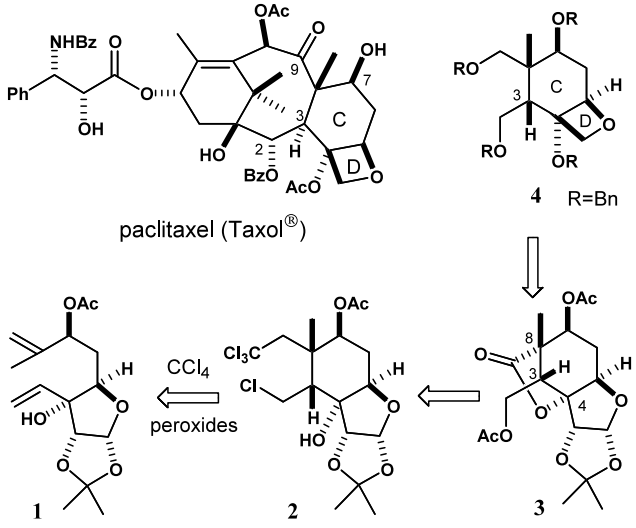
In the present study, synthesis of the CD ring system of paclitaxel through a peroxide-initiated carbon–halogen transfer reaction was accomplished, thereby demonstrating the usefulness of radical annulation strategy (Scheme 2).[6] This synthesis provides a novel route to chiral 3-*epi*-CD ring system,[†] which would be utilized as a key intermediate for the synthesis of paclitaxel.[7]

The conversion of readily available carbohydrates into functionalized carbocycles via radical reactions has been extensively studied.[8] In consideration of the intrinsic ability of D-glucose to produce the oxetane ring (D ring) of paclitaxel with the requisite absolute configuration, the synthesis was initiated with D-glucose derivative **1** (Scheme 3). [9–11]

Alcohol **5** prepared by a known procedure[12] was subjected to deoxygenation of the secondary hydroxy group to afford **6** in 62% overall yield. The trityl group of **6** was removed by sodium in liq. NH_3 to give diol **7** whose oxidation with Dess–Martin periodinane provided an aldehyde. Addition of isopropenylmagnesium bromide to the aldehyde gave the desired β-alcohol **8b** (54%) together with α-isomer **8a** (27%) in two steps from **7**. The minor α-alcohol **8a** was converted to **8b** in 74% overall yield via the Mitsunobu reaction followed by methanolysis. Acetylation of the β-alcohol **8b** proceeded to afford β-acetate **1** quantitatively. Using this acetate **1**, the atom-transfer radical annulation reaction under Kharasch conditions was carried out (Scheme 4).



Scheme 1.



Scheme 2.

Keywords: radicals and radical reactions; annulation; taxoids.

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† Paclitaxel numbering.

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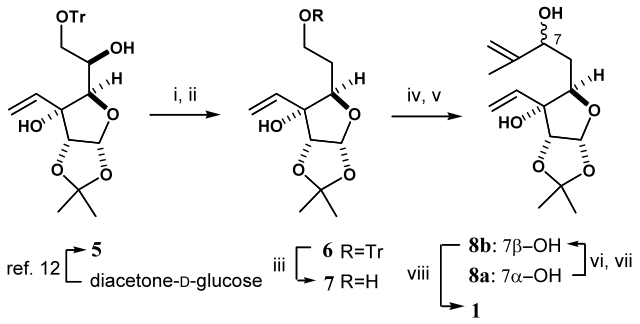

Scheme 3. *Reagents and conditions:* (i) thiocarbonyl diimidazole, DMAP, CH_2Cl_2, rt, 83%; (ii) Bu_3SnH, AIBN, toluene, reflux, 75%; (iii) Na, liq. NH_3, THF, −78°C, 70%; (iv) Dess–Martin periodinane, CH_2Cl_2, rt; (v) isopropenylMgBr, THF, 0°C, β-alcohol **8b** (54%), α-alcohol **8a** (27%), two steps; (vi) 4-nitrobenzoic acid, DEAD, PPh_3, toluene, −10°C; (vii) K_2CO_3, MeOH, rt, 74%, 2 steps; (viii) Ac_2O, Et_3N, CH_2Cl_2, rt, quant.

A solution of **1** and catalytic amount of benzoyl peroxide in carbon tetrachloride was heated to reflux for 3 h to provide cyclized products **2** and its C8-epimer in a ratio of 3:1 in ca. 80% yield,[13] along with a trace of unidentified by-product. Compound **2**, having the paclitaxel CD substructure, was found to possess halogen functionalities that would allow the multiple transformations in one step. Thus, on treating **2** with an excess of cesium acetate[14] in DMSO at 120°C for 45 min, chloroalkenyl ethers **9** was obtained in 72% yield along with diene **10** (16%).[15] This transformation established the stereochemistry of a quaternary carbon at C8 whose trichloroethyl substituent was found situated *syn* to the hydroxy group at C4. Other configurations of **9** were confirmed by NOE correlations.[16] Ozonization of chloroalkenyl ether **9** afforded lactone **3** in 65% yield. Reduction of **3** with $LiAlH_4$ and subsequent benzylation of the hydroxy groups in tetraol **11** provided **12** quantitatively. Hydrolysis of the isopropylidene acetal of **12** gave hemiacetals whose oxidative cleavage followed by the reduction with $LiAlH_4$ afforded diol **13** in 78% overall yield. Selective mesylation of diol **13** followed by the treatment with NaH in refluxing ether furnished the CD ring system of paclitaxel in quantitative yield.[17]

In conclusion, we have succeeded in synthesizing the CD ring system of paclitaxel via the atom-transfer radical annulation of diene **1** derived from diacetone-D-glucose. This synthesis features the concise construction of highly functionalized carbocycles through the introduction of multifunctional groups. The transformation clearly demonstrates the usefulness of the atom-transfer radical annulation reaction in increasing molecular complexity in only a few synthetic steps. Studies toward the total synthesis of paclitaxel based on this radical annulation strategy are presently under investigation.

Acknowledgements

We thank Ms. T. Koseki and Ms. A. Ohmae for conducting mass and NOE measurements.

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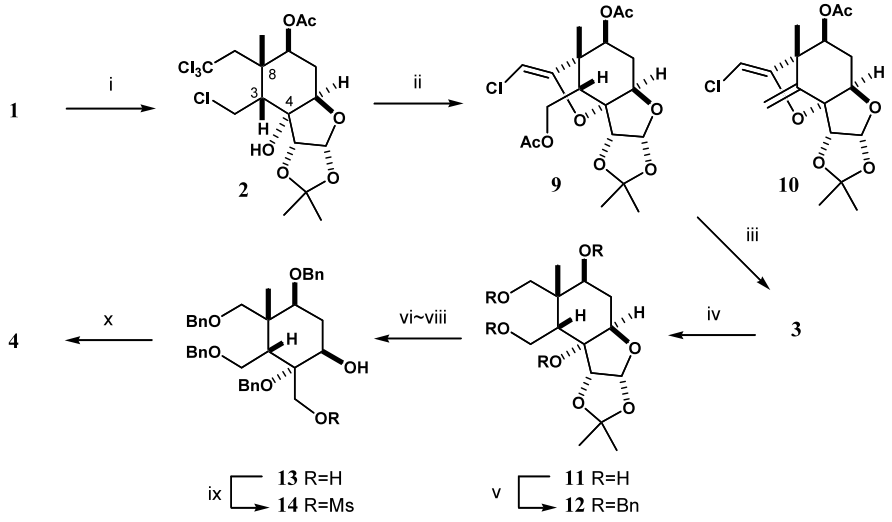

Scheme 4. *Reagents and conditions:* (i) cat. benzoyl peroxide, CCl_4, reflux, **2** (58%), C8-epimer (19%); (ii) 5 equiv. CsOAc, DMSO, 120°C, **9** (72%), **10** (16%); (iii) O_3, $NaHCO_3$, CH_2Cl_2, −78°C, then Me_2S, −78°C to rt, 65%; (iv) $LiAlH_4$, THF, 0–50°C; (v) NaH, BnBr, cat. Bu_4NI, DMF, 0–60°C, quant., two steps; (vi) aq. HCl, AcOH, THF, reflux; (vii) $Pb(OAc)_4$, CH_2Cl_2, rt; (viii) $LiAlH_4$, THF, 0°C, 78%, three steps; (ix) MsCl, Et_3N, CH_2Cl_2, rt; (x) NaH, Et_2O, reflux, quant., two steps.

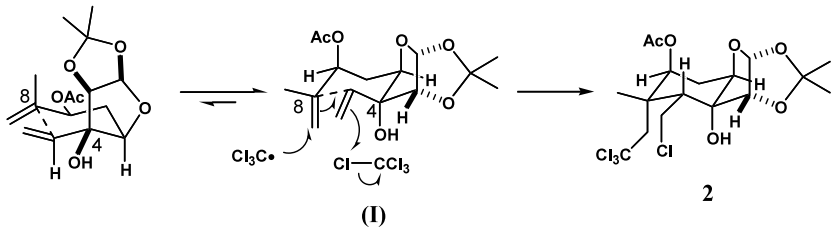

Figure 1.

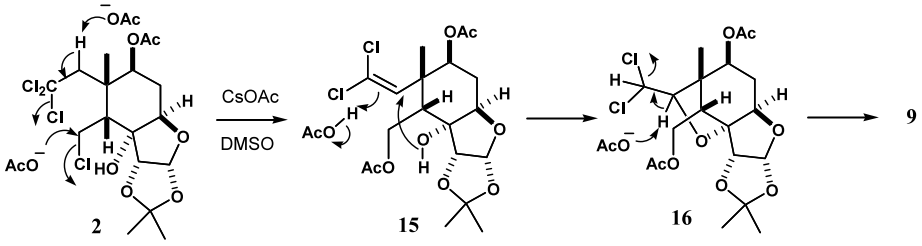

Figure 2.

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13. In contrast to the present case, a related cyclization of germacrene has been shown to selectively provide *trans*-decalin derivatives (Ref. 6b). The preferred formation of **2**, possessing the C8β-methyl group and the C3β-hydrogen, may be attributed to the conformationally flexible 1,7-diene system in **1** leading to the transition state (I) that alleviates steric interaction between the C8 methyl and C4 axial substituents (Fig. 1).

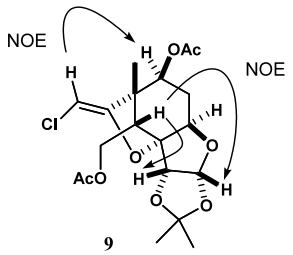

Figure 3.

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15. This alkenyl ether formation may proceed via the intramolecular cyclization of dichloro olefin **15** with a hydroxy group, followed by the elimination of hydrogen chloride (Fig. 2).
16. NOE interactions in **9** (Fig. 3).
17. Selected data: **2**: $[\alpha]_D^{23}$ +83.9 (*c* 0.329, $CHCl_3$); IR (neat) ν_{max} 3506, 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, 1H, $J=4.0$ Hz), 5.65 (t, 1H, $J=3.0$ Hz), 4.63 (d, 1H, $J=4.0$ Hz), 3.95 (dd, 1H, $J=12.7$, 3.5 Hz), 3.94 (m, 1H), 3.69 (dd, 1H, $J=12.7$, 3.1 Hz), 3.41 (d, 1H, $J=16.7$ Hz), 2.86 (d, 1H, $J=1.7$ Hz), 2.85 (d, 1H, $J=16.7$ Hz), 2.33 (m, 1H), 2.24 (ddd, 1H, $J=16.9$, 3.9, 3.0 Hz), 2.14 (m, 1H), 2.05 (s, 3H), 1.55 (s, 3H), 1.50 (s, 3H), 1.39 (s, 3H); MS(EI) *m/z*: 449 (M^+–15), 406, 290, 100 (100%); HRMS calcd for $C_{16}H_{21}Cl_4O_6$ 449.0094 (M^+–Me), found 449.0091.; **9**: $[\alpha]_D^{23}$ +80.5 (*c* 0.365, $CHCl_3$); IR (neat) ν_{max} 1744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (d, 1H, $J=3.5$ Hz), 5.15 (s, 1H), 4.86 (d, 1H, $J=3.5$ Hz), 4.79 (dd, 1H, $J=7.2$, 2.2 Hz), 4.43 (dd, 1H, $J=12.1$, 3.5 Hz), 4.27 (dd, 1H, $J=7.8$, 1.8 Hz), 4.11 (dd, 1H, $J=12.1$, 7.5 Hz), 2.65 (dd, 1H, $J=7.5$, 3.5 Hz), 2.38 (ddd, 1H, $J=$ 17.2, 7.8, 7.2 Hz), 2.09 (s, 3H), 2.08 (s, 3H), 1.88 (ddd, 1H, $J=17.2$, 2.2, 1.8 Hz), 1.61 (s, 3H), 1.38 (s, 3H), 1.21 (s, 3H); MS(EI) *m/z*: 416 (M^+), 401, 358; HRMS calcd for $C_{19}H_{25}ClO_8$ 416.1238 (M^+), found 416.1217.; **3**: $[\alpha]_D^{23}$ +117 (*c* 0.078, $CHCl_3$); IR (neat) ν_{max} 1794, 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, 1H, $J=3.5$ Hz), 5.01 (dd, 1H, $J=7.7$, 4.0 Hz), 4.82 (d, 1H, $J=3.5$ Hz), 4.57 (dd, 1H, $J=12.5$, 2.7 Hz), 4.32 (dd, 1H, $J=8.1$, 3.5 Hz), 4.15 (dd, 1H, $J=12.5$, 5.1 Hz), 2.75 (dd, 1H, $J=5.1$, 2.7 Hz), 2.60 (ddd, 1H, $J=16.6$, 8.1, 7.7 Hz), 2.10 (s, 3H), 2.09 (s, 3H), 1.89 (ddd, 1H, $J=16.6$, 4.0, 3.5 Hz), 1.60 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H); MS(EI) *m/z*: 369 (M^+–15) (100%), 326; HRMS calcd for $C_{17}H_{21}O_9$ 369.1185 (M^+–Me), found 369.1184.; **4**: $[\alpha]_D^{23}$ +58.0 (*c* 0.148, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.11 (m, 20H), 5.11 (dd, 1H, $J=6.1$, 3.1 Hz), 4.88 (d, 1H, $J=6.4$ Hz), 4.67 (d, 1H, $J=11.8$ Hz), 4.62 (d, 1H, $J=11.8$ Hz), 4.61 (d, 1H, $J=12.1$ Hz), 4.40–4.30 (m, 5H), 4.21 (d, 1H, $J=12.1$ Hz), 3.82 (dd, 1H, $J=10.5$, 9.0 Hz), 3.70 (dd, 1H, $J=9.0$, 4.7 Hz), 3.36 (dd, 1H, $J=4.5$, 4.0 Hz), 3.22 (s, 2H), 3.04 (dd, 1H, $J=10.5$, 4.7 Hz), 1.99 (ddd, 1H, $J=15.6$, 4.5, 3.1 Hz), 1.62 (ddd, 1H, $J=15.6$, 6.1, 4.0 Hz), 1.15 (s, 3H); MS(EI) *m/z*: 578 (M^+), 91 (100%); HRMS calcd for $C_{38}H_{42}O_5$ 578.3034 (M^+), found 578.3026.