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Efficient Synthesis of the Taxane C Ring by Fragmentation Reaction of a Bicyclo[2.2.2]octane Derivative[1]

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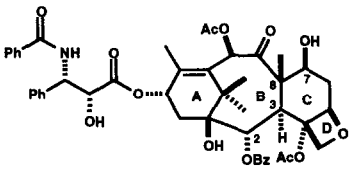
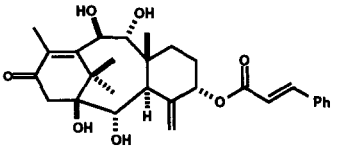
Abstract: Compounds **3**, the C/D ring moiety of paclitaxel without a 7-hydroxyl group, and **4**, the C ring moiety of *O*-cinnamoyltaxicin-I (**2**), were synthesized stereoselectively from methyl (*E,S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pentenoate (**5**) using the fragmentation reaction of bicyclo[2.2.2]-octane derivative **9** as a key step to give **10**. © 1997 Elsevier Science Ltd.

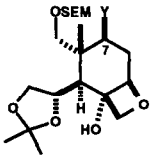
Taxol® (paclitaxel) (**1**), a typical taxane diterpene, is one of the most attractive synthetic targets in organic chemistry because of its unique structural features, as well as its antileukemic and tumor-inhibiting activity.[2] Recently, we described a useful intramolecular nitrile oxide cyclization reaction for construction of the taxane A/B ring system.[3] In connection with our synthetic studies on the taxane class of diterpenes, such as **1** and *O*-cinnamoyltaxicin-I (**2**), by applying this cyclization, we acquire efficient access to highly functionalized cyclohexane derivatives corresponding to the C ring system of target molecules.[4] In this communication, we would like to report a stereocontrolled synthesis of **3** (Y=H) and **4** which involves the fragmentation reaction of bicyclo[2.2.2]octane derivative **9** as a crucial step to give **10**.



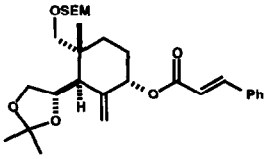
paclitaxel (1)



***O*-cinnamoyltaxicin-I (2)**



3 Y=H



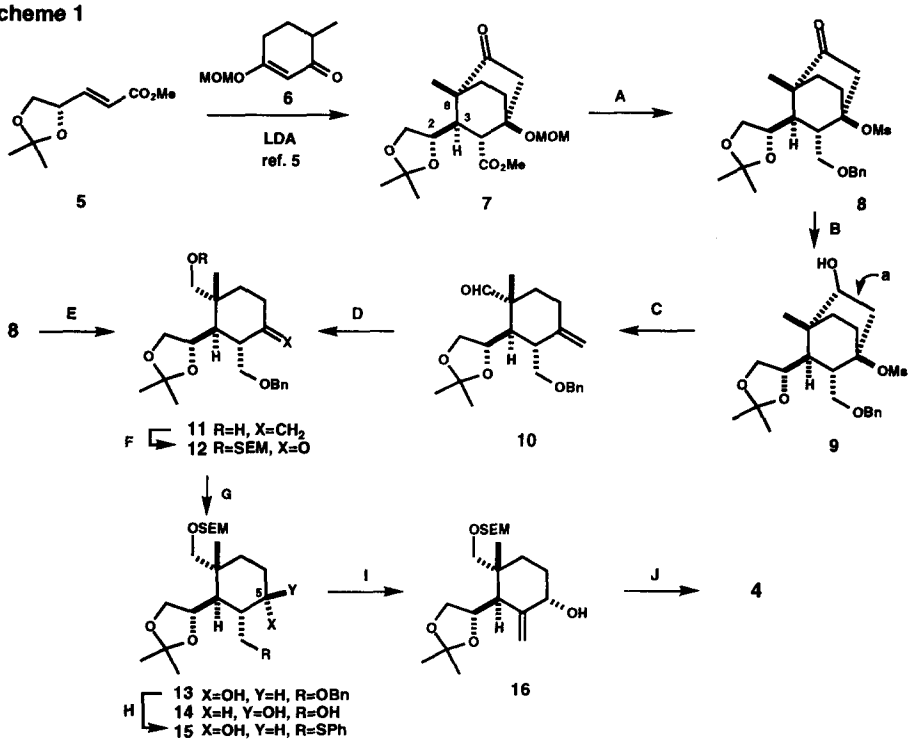
4

Optically active bicyclo[2.2.2]octane derivative **7**,[5] prepared by diastereoselective sequential Michael reaction of the kinetic enolate of enone **6** with α,β-unsaturated ester **5** readily available from D-mannitol, was chosen as the starting material, since it provides the requisite three chiral centers (C-2, C-3 and C-8) in **1** and **2**.

Keto ester **7** was converted into keto mesylate **8** by a five-step sequence in 54% overall yield: i) $LiAlH_4$ reduction giving the corresponding diol; ii) selective benzylation of the primary hydroxyl group; iii) PCC oxidation of the secondary hydroxyl group; iv) selective deprotection of the methoxymethyl (MOM) group; and v) mesylation of the resulting tertiary hydroxyl group (Scheme 1). Hydroxy mesylate **9**, the precursor of the fragmentation reaction, was obtained by $NaBH_4$ reduction of **8** as a single isomer. Cleavage of the C-C bond **a** was conducted by treatment of **9** with 1.5 equiv. of *t*-BuOK in *t*-BuOH for 1h at 25°C to give pentasubstituted cyclohexane **10**, which was then reduced with $NaBH_4$ in MeOH to obtain alcohol **11** ($[\alpha]_D^{25}$ +10.4° (*c* 1.2, $CHCl_3$))[6] in 76% overall yield from **8**. After some attempts to obtain this compound more conveniently, it was found that **11** was synthesized from **8** in the following one-pot process which involves a sequential reduction-fragmentation-reduction reaction. To a cold (0°C) solution of keto mesylate **8** in MeOH was added 2.0 equiv. of $NaBH_4$. After 5 min, DMSO and 1.5 equiv. of *t*-BuOK were added, and the mixture was stirred for 10 min at 25°C to furnish **11** in 93% yield.

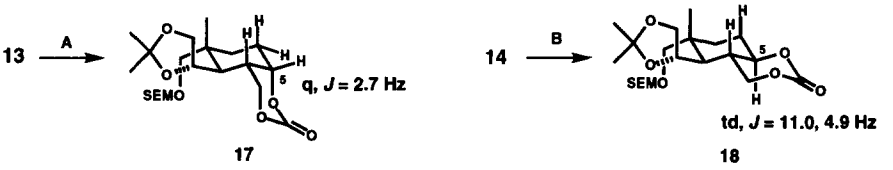
With the desired pentasubstituted cyclopentane derivative in hand, functionalization of the C ring was

Scheme 1



Reagents: A. 1) $LiAlH_4$, THF, rt, 2) BnBr, NaH, THF-DMF (3:1), 0°C, 3) PCC, 4ÅMS, rt, 4) TsOH, acetone-H_2O (99:1), rt, 5) MsCl, pyridine, rt, 54% (5 steps); **B**. $NaBH_4$, MeOH, 0°C, 96%; **C**. *t*-BuOK, *t*-BuOH, rt, 81%; **D**. $NaBH_4$, MeOH, 0°C, 98%; **E**. $NaBH_4$, *t*-BuOK, MeOH-DMSO, 93%; **F**. 1) SEMCl, *i*-Pr_2NEt, 2) OsO_4, NMO, CH_3CN-H_2O (3:1), then $NaIO_4$, sat.$NaHCO_3$, 0°C, 76% (2 steps); **G**. L-Selectride, THF, -78°C, 98%; **H**. 1) Na, NH_3-EtOH (3-1), -34°C, 2) PhSSPh, Bu_3P, pyridine, 60°C, 81% (2 steps); **I**. 1) MCPBA, CH_2Cl_2, -78°C, 2) *i*-Pr_2NEt, *o*-dichloro-benzene, 180°C, 83% (2 steps); **J**. cinnamoyl chloride, pyridine, 20°C, 92%.

conducted. Protection of the hydroxyl group in **11** as the 2-(trimethylsilyl)ethyloxymethyl (SEM) ether, followed by oxidative cleavage of *exo*-olefin gave ketone **12**. Alcohol **13** having the desired 5α-hydroxyl group[7] was obtained by reduction of **12** with L-selectride in THF at -78°C in 98% yield as a single isomer, whereas $NaBH_4$ reduction of **12** in MeOH gave a 1:1.5 mixture of **13** and the corresponding α-hydroxyl isomer and Na-liquid ammonia reduction of **12** gave 5β-alcohol **14** exclusively. The configuration of the hydroxyl group generated at C-5 in **13** and **14** was determined by comparison of the coupling constants in ^{1}H-NMR of the C-5 proton (4.7 ppm, q, *J*=2.7 Hz) in carbonate **17** derived from **13** with that (4.1 ppm, td, *J*=11.0, 4.9 Hz) in carbonate **18** derived from **14**.

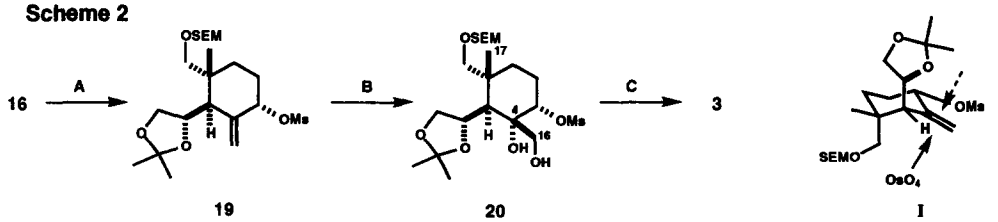


Reagents: A. 1) Li, liq.NH_3-EtOH (3:1), -78°C; 2) carbodiimidazole, NaH, THF-DMF (3:1), 25°C, 59% (2 steps); **B**. carbodiimidazole, THF, 50°C, 63%.

Construction of the C ring system **4** from **13** via formation of the *exo*-olefin and esterification of the secondary hydroxyl group was accomplished as follows. Removal of benzyl ether from **13** by Na-liquid ammonia reduction, followed by selective phenylsulfination of the primary hydroxyl group with phenyl disulfide and tributylphosphine in pyridine at 60°C gave **15**. Oxidation of the sulfide with *m*-chloroperbenzoic acid at -78°C and subsequent pyrolysis at 180°C in the presence of *N,N*-diisopropylethyl amine yielded **16**, whose secondary hydroxyl group was acylated by treatment with cinnamoyl chloride in pyridine to give **4** ($[\alpha]_D^{25}$ +41.3° (*c* 0.8, $CHCl_3$))[8] in 62% overall yield.

Compound **3** bearing an oxetane moiety, corresponding to the D ring in paclitaxel, was synthesized from **16** via mesylate **20** (Scheme 2). Mesylation of the allylic hydroxyl group in **16**, followed by oxidation of the *exo*-olefin with OsO_4 and pyridine in Et_2O gave **20** having the desired β-oriented hydroxymethyl group at C-4 in 57 % yield as a single isomer. The configuration of the newly introduced hydroxymethyl group was confirmed by NOE correlation between the methyl proton at C-17 and the methylene proton at C-16. The observed stereochemical outcome of the dihydroxylation reaction can be rationalized on the basis of the preferred conformation **I**[9] of allyl mesylate **19**, in which the 1,3-dioxolan group covers the β-face of the olefin moiety. Finally, treatment of mesylate **20** with 1,5-diazabicyclo[4.3.0]non-5-ene in DME for 1.5 h at 85°C gave oxetane **3** ($[\alpha]_D^{25}$ +10.0 (*c* 0.70, $CHCl_3$)).[11]

Scheme 2



Reagents: A. MsCl, DMAP, pyridine, rt; **B**. OsO_4, pyridine, Et_2O,[2b] 57% (2 steps); **C**. DBN, DME, 85°C, 78%.

In summary, the taxane precursors **4** (C ring system of *O*-cinnamoyltaxicin-I) and **3** (C/D ring system of paclitaxel without a C-7 hydroxyl group) were synthesized stereoselectively from methyl (*E,S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-pentenoate (**5**) using the sequential reduction-fragmentation-reduction reaction of keto mesylate **8**. We are currently investigating the total synthesis of *O*-cinnamoyltaxicin-I and 7-dehydroxy-paclitaxel by use of **4** and **3**, respectively, in this laboratory.

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1. This paper is dedicated to Prof. Yasuji Yamada on the occasion of his 60th birthday.
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6. Spectoscopic data for compound **11**. IR (film) 3462, 1645 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26-7.35 (5H, m), 4.81 (2H, m), 4.54 (1H, d, *J*=12.0 Hz), 4.49 (1H, d, *J*=12.0 Hz), 4.30 (1H, td, *J*=8.0, 3.4 Hz), 3.95 (1H, t, *J*=8.0 Hz), 3.73 (1H, t, *J*=8.0 Hz), 3.61 (1H, dd, *J*=9.8, 6.4 Hz), 3.54 (1H, dd, *J*=9.8, 6.4 Hz), 3.46 (1H, d, *J*=11.3 Hz), 3.34 (1H, d, *J*=11.3 Hz), 2.84 (1H, q, *J*=6.4 Hz), 2.17-2.28 (2H, m), 1.95 (1H, dd, *J*=6.4, 3.4 Hz), 1.55 (1H, m), 1.45 (1H, m), 1.42 (3H, s), 1.31 (3H, s), 0.97 (3H, s); HREIMS calcd. for $C_{22}H_{32}O_4$ (M^+) 360.2300, found 360.2296.
7. The numbering in this paper is accordance with that for taxanes.
8. Spectoscopic data for compound **4**. IR (film) 1714, 1637 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, d, *J*=16.1 Hz), 7.52-7.53 (3H, m), 7.39-7.44 (2H, m), 6.50 (1H, d, *J*=16.1 Hz), 5.89 (1H, m), 5.11 (1H, m), 4.72 (1H, m), 4.67 (1H, d, *J*=6.6 Hz), 4.64 (1H, d, *J*=6.6 Hz), 4.35 (1H, ddd, *J*=7.7, 5.5, 3.3 Hz), 3.89 (1H, dd, *J*=7.7, 5.5 Hz), 3.71(1H, t, *J*=7.7 Hz), 3.58-3.62 (2H, m), 3.48 (1H, d, *J*=9.2 Hz), 3.30 (1H, d, *J*=9.2 Hz), 2.40 (1H, m), 1.97-2.05 (2H, m), 1.55-1.57 (2H, m), 1.50 (3H, s), 1.37 (3H, s), 1.10 (3H, s), 0.92-0.96 (2H, m), 0.03 (9H, s); HREIMS calcd. for $C_{29}H_{44}O_6Si$ (M^+) 516.2906, found 516.2895.
9. The conformation **I** of **19** was obtained by MM2 calculation using MacroModel V4.5.[10]
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11. Spectroscopic data for compound **3**. IR (film) 3446 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.72 (1H, dd, *J*=6.3, 3.8 Hz), 4.69 (1H, d, *J*=8.2 Hz), 4.64 (1H, d, *J*=6.6 Hz), 4.62 (1H, d, *J*=6.6 Hz), 4.44 (1H, d, *J*=8.2 Hz), 4.24 (1H, dt, *J*=8.3, 6.1 Hz), 4.19 (1H, s), 4.14 (1H, dd, *J*=8.3, 6.1 Hz), 3.72 (1H, t, *J*=8.3 Hz), 3.54-3.61 (2H, m), 3.19 (1H, d, *J*=9.3 Hz), 3.15 (1H, d, *J*=9.3 Hz), 1.95 (1H, m), 1.89 (1H, d, *J*=8.3 Hz), 1.82 (1H, m), 1.61-1.69 (2H, m), 1.42 (3H, s), 1.34 (3H, s), 1.10 (3H, s), 0.91-0.95 (2H, m), 0.02 (9H, s); HREIMS calcd. for $C_{19}H_{35}O_6Si$ (M^+-CH_3) 387.2204, found 387.2202.

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