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A New Efficient Synthesis of Taxol A-ring Synthon via Two Aldol Condensations**

Chang-Qing Wei, Xiang-Rong Jiang, Yu Ding*

Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Rd., Shanghai 200032, China

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Abstract: An efficient stereocontrolled synthesis of a taxol A-ring synthon using two aldol reactions as key steps is presented.

Keywords: taxol, synthesis, aldol reaction.

INTRODUCTION

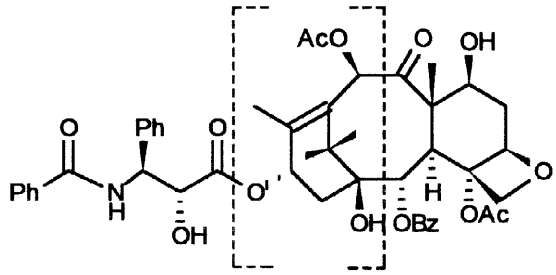

Fig. 1 Taxol 1

Taxol 1, a clinically useful antitumor agent, since it was isolated[1] from the Pacific yew tree, has attracted considerable interest from synthetic organic chemists owing to its remarkable anticancer activity and its limited supply. Efficient routes to taxane diterpenoids[2] have recently been described and many more are in progress[3]. However, convenient access to the fully functionalized A-ring, C-ring and the construction of the sterically congested eight-membered B-ring remain challenges in taxol synthesis.

** In memory of Prof. Wang Yu.

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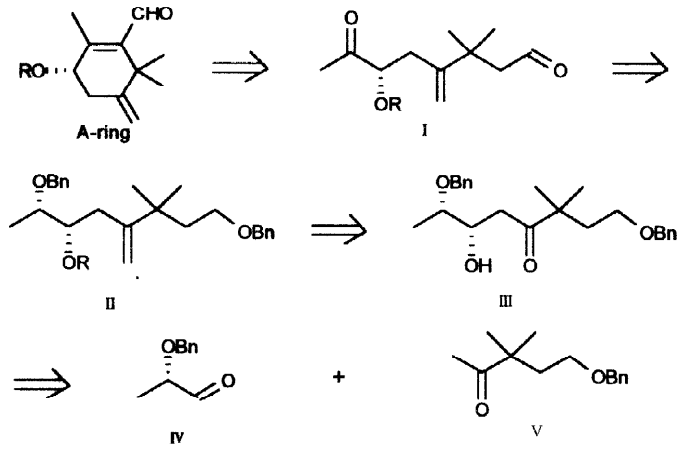
Among the syntheses of taxol A-ring, a multisubstituted cyclohexene ring (see Fig.1), the Diels-Alder route has been the most popular one, adopted by many groups.[4] In addition, Kitagawa's ring enlargement[5] and Frejd's intramolecular cyclization routes[6] are quite attractive. Herein, we report a route to taxol A-ring synthon based on stereocontrolled aldol reactions, in which a stereoselective intermolecular aldol reaction and a regioselective intramolecular aldol reaction are used successfully.

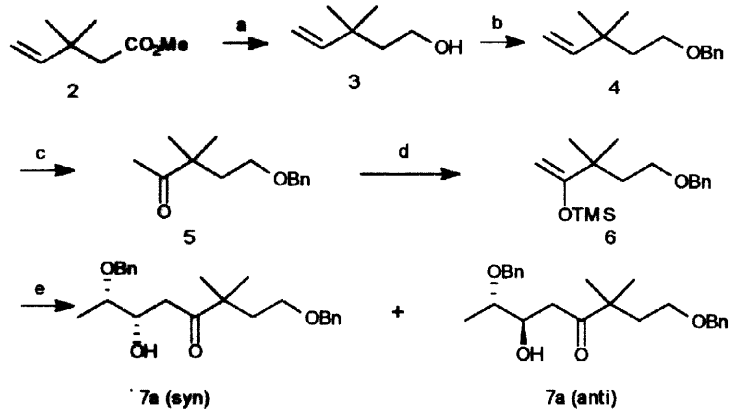
RESULTS AND DISCUSSION

The retrosynthetic disconnection outlined in Scheme 1 uses the 1,7-ketoaldehyde I as the crucial intermediate which could be traced to the two key building blocks IV and V. The former can be readily obtained from ethyl lactate, and the latter can also be easily prepared as shown in Scheme 2. The two aldol reactions, one intramolecular and the other intermolecular, would be key steps.



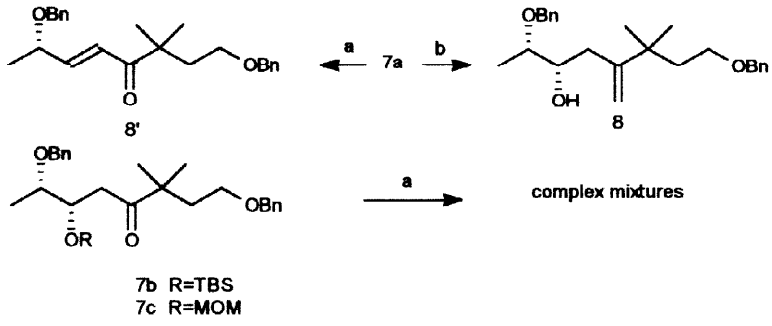
Scheme 1

The reaction proceeded as below (Scheme 2). Starting material 2 can be prepared by several procedures[7] and is also available commercially. Reduction of 2 with LAH gave 3 quantitatively. Hydroxyl protection of compound 3 with NaH/BnBr in DMF afforded its benzyl ether 4 in 92% yield. Wacker oxidation of 4 with O_2 /$PdCl_2$ in DMF-H_2O (7:1) solution at room temperature for 24 hr. produced ketone 5 in 83% yield, which was then transformed to its silyl enol ether form 6 upon treatment with LDA/Me_3SiCl/Et_3N in CH_2Cl_2 at -78°C. Compound 6 was used directly without further purification. Finally, the Lewis acid catalytic chelation-controlled aldol addition of silyl enol ether 6 to 2-benzyloxypropanal[8] gave the desired adduct 7a with excellent stereoselectivity (syn:anti > 99:1).[9]



Scheme 2 a. LAH, Et_2O, 92%. b. NaH, BnBr, DMF, 92%. c. O_2, $PdCl_2$, CuCl, DMF/H_2O, 83%. d. LDA, THF, -78 ° C; TMSCl, NEt_3, 95%. e. 2-benzyloxypropanal,$TiCl_4$, CH_2Cl_2, -78 ° C, 97% (syn : anti :- 99 : 1).

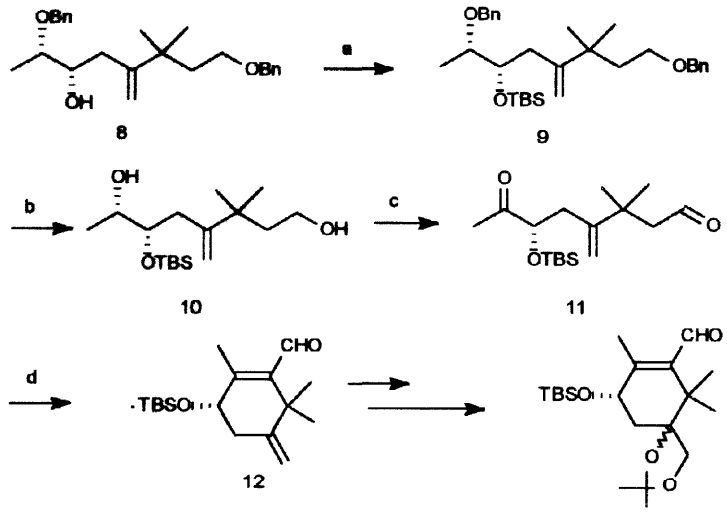
Difficulties were encountered when we attempted the deoxy-methylenation of the carbonyl group in compound 7a (Scheme 3). Treatment of 7a under nitrogen with 2.8 equiv. of the active Wittig ylide derived from Ph_3PCH_3I, t-BuOK in PhH at room temperature for 12 hr. gave no desired methylenic product 8, the main product was the α,β-unsaturated ketone 8'which was formed through undesired dehydration of the β-hydroxyketone in compound 7a.



Scheme 3 a. Ph_3PCH_3I, t-BuOK, PhH, r.t., 12h. b. Zn/TiCl 4/CH_2I_2, THF, r.t., 12h, 88%.

Protection of the hydroxyl group also did not lead to the desired compound . When 7b and 7c, protected by TBS (TBSCl, imidazole, DMF, r.t., overnight) and MOM ($MeOCH_2OMe$, P_2O_5, $CHCl_3$, r.t., overnight) respectively, were treated with $Ph_3P{=}CH_2$, only complex mixtures were obtained in both cases, even though TBS and MOM are compatible with base. After this failure, we tried $Zn/TiCl_4/CH_2I_2$ as methylenation

reagents. Promisingly, compound 7a, with hydroxyl group unmasking, upon treatment with $Zn/TiCl_4/CH_2I_2$ (3:1:1.5) under nitrogen at room temperature overnight generated the single product 8 in 88% yield.



Scheme 4 a. TBSCl, imidazole, DMF, 50 °C, 10h, 95%. b. $Li/EtNH_2$, THF, -78 °C, 15min., 78%. c. Swern oxidation. d. cat. PTSA, piperidine, r.t., overnight, 62%.

Finally, as shown in Scheme 4, protection of the hydroxyl group in compound 8 with t-butyldimethylsilyl ether gave compound 9 in good yield. Removal of the benzyl protecting groups in dibenzyl ether 9 under nitrogen with $Li/EtNH_2$ at -78°C for 15 min. gave diol 10 in 78% yield. Subsequent Swern oxidation of diol 10 afforded dicarbonyl compound 11 in 93% yield. Without further purification, ketoaldehyde 11 was directly converted to the six-membered ring structure 12 through a high regioselective intramolecular Aldol condensation reaction under mild conditions (cat.PTSA, piperidine, r.t., overnight). We noted that, when we adopted the Terashima's intramolecular aldol cyclization method[10] (HOAc, piperidine, PhH, r.t., overnight), a complex mixture was produced; we thought that partial removal of the silyl protecting group and/or subsequent dehydration may have occurred.

Compound 12, a general taxol A-ring synthon, containing the complete carbon framework and fully differentiated functionalities, which allows selective introduction of carbon chain moieties at C2 and C10, can be a useful intermediate in the construction of the taxol tricyclic skeleton.

In summary, we developed an efficient regioselective and stereoselective route to taxol A-ring from cheap and accessible starting materials, which could be further used for providing chiral A-ring synthon easily and economically in the synthesis of taxol and its analogs.

EXPERIMENTAL

General methods. Infrared spectra were recorded on a Shimadzu IR-440 spectrometer and only the strongest and structurally most important peaks were listed in cm^{-1}. ^1H NMR spectra were obtained on a EM 390A(90 MHz) or on a Bruker AM 300(300 MHz) spectrometer using TMS as internal standard. Mass spectra were run on a Finnigan 4021 and HP5989A spectrometer. HRMS were recorded on Finnigan MAT spectrometer. Flash chromatography was carried out using silica gel (300-400 mesh made in Yantai, China).

3,3-Dimethyl-4-pentenol (3):

To the suspension of LAH (5.78g, 0.125mol) in ether (500ml) was added 2 (15.6g, 0.1mol) at 0°C,then the suspension was allowed to warm to room temperature and stirred for 1 h. Aqueous NaOH was added to quench the reaction. The mixture was filtered through a pad of celite and the solid was washed with ether, the combined organic fractions were washed with saturated aqueous NaCl,dried over Na_2SO_4. After removal of solvent, the residue was purified by flash column chromatography (petroleum : ethyl acetate = 2 : 1) to give the title compound 3 (10.5g, 92%) as a colorless oil; IR 3385, 3090, 2995, 1650, 1478, 1385, 1260, 1108, 800; ^1H-NMR(90 MHz, CCl_4) 1.08 (6H, s), 1.55 (2H, t), 3.48 (2H, t), 4.80 (1H, s), 4.95 (1H, d), 5.80 (1H, dd); EIMS m/z 113 (M^+-1), 97, 91, 81.

3,3-Dimethyl-5-benzyloxy-1-pentene (4):

To a stirred solution of 3 (5.71g, 50mmol) in DMF (100ml), NaH (2.4g, 60mmol) was added in portions at 0°C, then the mixture was allowed to warm to room temperature and stirred for 0.5 h, after which a solution of benzyl bromide (7.13ml, 60mmol) in DMF (20ml) was added dropwise. After further stirring at room temperature for 3 h, the mixture was poured into pre-cooled water (200ml) and extracted with ether (3 × 50ml), the combined organic layer was washed with 10%HCl and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 20 : 1) gave the title compound 4 (9.3g, 92%) as a colorless oil; IR 3110, 3000, 2940, 1650, 1460, 1370, 1110, 920, 740, 702; ^1H-NMR (300 MHz, $CDCl_3$) 1.04 (6H,s), 1.70 (2H, t, J 7.4), 3.50 (2H, t, J 7.4), 4.48 (2H, s), 4.90 (1H, s), 4.97 (1H, m), 5.82 (1H, dd, J 10.0, 17.3), 7.35 (5H, m); EIMS m/z 203 (M^+-1), 177, 149, 105, 91.

3,3-Dimethyl-5-benzyloxy-2-pentanone (5):

O_2 was bubbled through a stirred solution of $PdCl_2$ (0.9g, 5mmol), CuCl (2.23g, 22.6mmol) in 140ml of DMF and 20ml of H_2O for 2 hr. Compound 4 (2.3g, 11.3mmol) was added to the solution and O_2 was bubbled through for a additional 60 hr. at room temperature. Water (100ml) was added to dilute the reaction mixture and the aqueous layer was extracted with ether (3×150ml), the combined organic layer was concentrated and purified by flash column chromatography (petroleum : ethyl acetate = 20 : 1) to give the title compound 5 (2.1g, 83%) as a pale yellow oil; IR 2940, 1700, 1460, 1360, 1120, 1100, 770, 740; ^1H-NMR (300 MHz,

$CDCl_3$) 1.12 (6H, s), 1.88 (2H, t, J 6.55), 2.12 (3H, s), 3.47 (2H, t, 6.55), 4.41(2H, s), 7.28 (5H, m); EIMS m/z 221 (M^++1), 176, 113, 91.

3,3-Dimethyl-5-benzyloxy-2-trimethylsilyloxy-1-pentene (6):
Butyllithium (3.5ml, 5.5mmol) was added to a solution of i-pr_2NH (0.77ml, 5.5mmol) in THF (20ml) at -78°C, then the mixture was allowed to warm to room temperature and stirred for 20 minutes. The mixture was then recooled to -78°C, 5 (1.1g, 5mmol) was added and stirred for 1h, then TMSCl (1.1ml, 8.5mmol) was added and stirred for 10 minutes. Saturated aqueous $NaHCO_3$ was added and the mixture was warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3×50ml), the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 40 : 1) gave the title compound 6 (1.42g, 96.5%) as a brown oil; ^{1}H-NMR (90 MHz, CCl_4) 0.2 (9H, s), 1.08 (6H, s), 1.73 (2H, t), 3.42 (2H, t), 4.04 (2H, d), 4.46 (2H,s), 7.28 (5H, s).

3,3-Dimethyl-1,7-dibenzyloxy-6-hydroxy-4-octanone (7a):
A solution of 2-benzyloxypropanal (0.36g, 2.2mmol) and 6 (0.6g, 2mmol) in CH_2Cl_2 (4ml) was cooled to -78°C and $TiCl_4$ (0.33ml, 3mmol) was added dropwise.The mixture was stirred for 2h and saturated aqueous $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3×10ml) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4, removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 10 : 1) gave the title compound 7a (0.68g, 88%) as a colorless oil; IR 3560, 2900, 1700, 1450, 1360, 1100, 740, 690; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.12 (6H, s), 1.13 (3H, d, J 6.27), 1.88 (2H, m), 2.46 (1H, br.s), 2.67 (2H, m), 3.46 (3H, m), 4.0 (1H, m), 4.40 (2H, s), 4.42 (1H, d, J 11.9), 4.60 (1H, d, J 11.9), 7.28 (10H,m); EIMS m/z 385 (M^++1), 367 (M^++1−H_2O), 259, 141, 91; HREIMS: calcd. for $C_{24}H_{32}O_4$ m/z (M^+-1) 383.2222, found 383.2188.

3,3-Dimethyl-1,7-dibenzyloxy-6-hydroxy-4-methylene octane (8):
Diiodomethane (0.12ml, 1.5mmol) was added at 25°C to a stirring suspension of zinc (0.3g, 4.5mmol) in THF (4ml) under nitrogen. After 30 min.,a dichloromethane solution of $TiCl_4$ (1.0M, 1ml, 1.0mmol) was added at 0°C and the resulting dark brown mixture was stirred at 25°C for 30 min.. A solution of ketone 7a (0.384g, 1.0mmol) in THF (2ml) was added dropwise at 25°C. After being stirred at 25°C overnight, the mixture was diluted with ether and the organic layer was washed with 1N HCl solution and brine. Removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 5 : 1) gave the title compound 8 (0.34g, 88%) as a colorless oil; IR 3467, 3090, 3032, 2969, 1634, 1454, 1365, 1097, 736, 697; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.08 (3H, s), 1.10 (3H, s), 1.25 (3H, d, J 6.2), 1.76 (2H, m), 2.20 (2H, m), 2.49 (1H, br.s), 3.42 (2H, m), 3.50 (1H, m), 3.75 (1H,m), 4.45 (2H,s), 4.48 (1H,d, J 11.8), 4.68 (1H,d, J 11.8), 4.98 (2H,s), 7.34 (10H,m); FABMS m/z 383 (M^++1), 405 (M^++Na).

3,3-Dimethyl-6-t-butyldimethylsilyloxy-4-methylene-1,7-dibenzyloxy octane (9):
To a solution of 8 (0.315g, 0.82mmol) in DMF (0.5ml)°C was added imidazole (0.168g, 2.46mmol), TBSCl (0.186g, 1.23mmol). The mixture was allowed to stand overnight at 50°C. Water (2ml) was added to quench the reaction and the aqueous layer was extracted with ether (3 × 5ml),the combined organic layer was washed with brine,dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 10 : 1) gave the title compound 9 (0.37g, 92%) as a colorless oil; IR 3090, 3030, 2980, 2880, 1635, 1460, 1365, 1260, 1095, 840, 740, 700; ^{1}H-NMR (300 MHz, $CDCl_3$) 0.01 (6H, d), 0.88 (9H, s), 1.08 (6H, s), 1.18 (3H, d, J 6.3), 1.78 (2H, m), 2.05 (1H, dd, J 9.2, 15.0), 2.40 (1H, dd, J 1.2, 15.0), 3.40 (2H, t, J 7.5), 3.58 (1H, m), 3.97 (1H, m), 4.46 (2H, s), 4.58 (1H, d, J 12.1), 4.62 (1H, d, J 12.1), 4.89 (1H, s), 4.92 (1H, d, J 1.1), 7.34 (10H, m); EIMS m/z 496 (M^+), 481, 361, 331, 279, 181, 131, 91.

3,3-Dimethyl-6-t-butyldimethylsilyloxy-4-methylene-1,7-octanediol (10):
Li (0.088g,12.5mmol) was added in portions to $EtNH_2$ (10ml) at -78°C under nitrogen. After the characteristic deep blue color persisted, a solution of 9 (0.124g, 0.25mmol) in THF (5ml) was added. After 15 min., the blue color was discharged by the careful addition of aqueous NH_4Cl and the aqueous layer was extracted with ethyl acetate (3 × 10ml), the combined organic layer was washed with brine,dried over Na_2SO_4, removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 2 : 1) gave the title compound 10 (0.062g, 78%) as a colorless oil; IR 3400, 3100, 3000, 1638, 1462, 1380, 1260, 1080, 840, 780; ^{1}H-NMR (300 MHz, $CDCl_3$) 0.08 (6H, d), 0.88 (9H, s), 1.04 (3H,s), 1.09 (3H, s), 1.18 (3H, d, J 6.1), 1.57 (1H, m), 1.74 (1H, m), 2.16 (2H, m), 3.22 (1H, m), 3.58 (2H, m), 3.62 (1H, m), 5.00 (1H, s), 5.03 (1H, s). EIMS m/z 317 (M^++1), 299, 281, 185, 173, 159, 131.

3,3-Dimethyl-4-methylene-6-t-butyldimethylsilyloxy-7-oxo octanal (11):
A stirred solution of oxalyl chloride (0.3ml, 3.2mmol) in CH_2Cl_2 (10ml) was treated dropwise with a solution of DMSO (0.5ml,6.7mmol) in CH_2Cl_2 (5ml) at -78°C, the mixture was stirred for 10 minutes, then 10 (0.41g, 1.3mmol) was added. After further stirring for 1h, triethylamine (1.85ml) was added. The mixture was stirred for a further 10 minutes, then was allowed to warm to room temperature, water (10ml) was added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (3×10ml), the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4.

2,6,6-Trimethyl-3-t-butyldimethylsilyloxy-5-methylene cyclohexene carboxaldehyde (12):
To a solution of 11 (156mg, 0.5mmol) in benzene (10ml) was added piperidine (0.05ml, 0.5mmol)and p-toluenesulfonic acid (8.6mg, 0.05mmol). The mixture was allowed to stand overnight at room temperature and then was washed with 10%HCl, dilute aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of solvent and purification by flash column chromatography (petroleum : ethyl acetate = 30 : 1) gave the title compound 12 (85.2mg, 58%) as a colorless oil; IR 2980, 2850, 1725, 1638, 1470, 1360, 1260, 1100, 840,

780; ^{1}H-NMR (300 MHz, $CDCl_3$) 0.03 (6H, s), 0.88 (9H, s), 1.19 (6H, s), 2.17 (2H, s), 2.36 (3H, d, J 6.1), 4.17 (1H, t, J 6.1), 5.01 (1H, s), 5.03 (1H, s), 9.64 (1H, t, J 2.7); EIMS m/z 295 (M^++1), 255, 237, 209, 199, 191, 163, 143, 135, 119, 107, 75; **HREIMS: calcd.** for $C_{17}H_{30}O_2Si$ m/z 294.2015 found 294.2036.

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