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A Short Synthesis of the A-ring of Taxol

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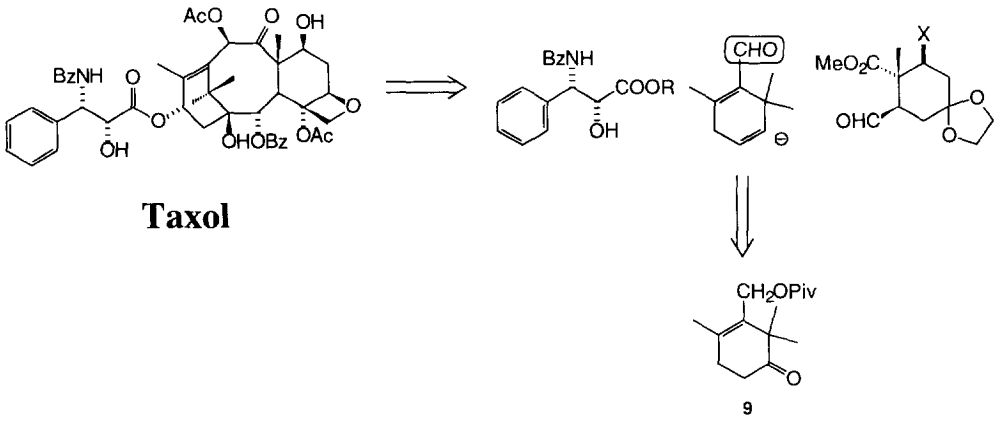
Abstract: A short synthesis of the taxol A-ring building block starting from an inexpensive mixture of E- and Z- citrals is described.

INTRODUCTION

Taxol, a diterpene isolated from the bark of the Pacific Yew tree,[1] has shown high activity against several tumor cell lines. Originally, taxol received little attention because of its low natural abundance. Since the discovery of its unique mechanism of action,[2] taxol has aroused renewed interest among synthetic organic chemists.[3] The efforts of more than 30 research groups have culminated in the recent total syntheses by the groups of Nicolaou and Holton.[4] The problem of low natural availabily of taxol which retarded clinical trials seems to be solved by semisynthetic approaches utilising 10-deacetylbaccatin III and a synthetic side chain equivalent.[3] Even though taxol was recently approved by FDA[5] for the treatment of refractive ovarian cancer it is still not a perfect drug: e.g. the solubility and toxicity pose serious problems. Therefore, simpler analogs with better solubility and improved therapeutic index are being sought for.[6] Taxotere®, a semisynthetic taxol derivative, is already undergoing clinical trials.[7]

We have also started a program aiming at the total synthesis of taxol and its analogs. The retrosynthetic analysis is shown in the Scheme 1. Our convergent plan relies on inducing all chirality of the molecule from the chiral C-ring building block. There is no need for chiral centers in the A-ring building block because we plan to introduce them later in synthesis, likewise, the C-13 oxygen can be introduced at a later stage. We believe that our approach is particularly well suited for the preparation of simpler analogs which could show better activity against tumor cells. In connection with this work we have recently published a short enantioselective synthesis of the taxol and taxotere side chains and we are currently working on improving it.[8] In this paper we present a short efficient approach to the A-ring precursor **9** for the taxanes starting from a commercially available mixture of *E*- and *Z*-citrals.



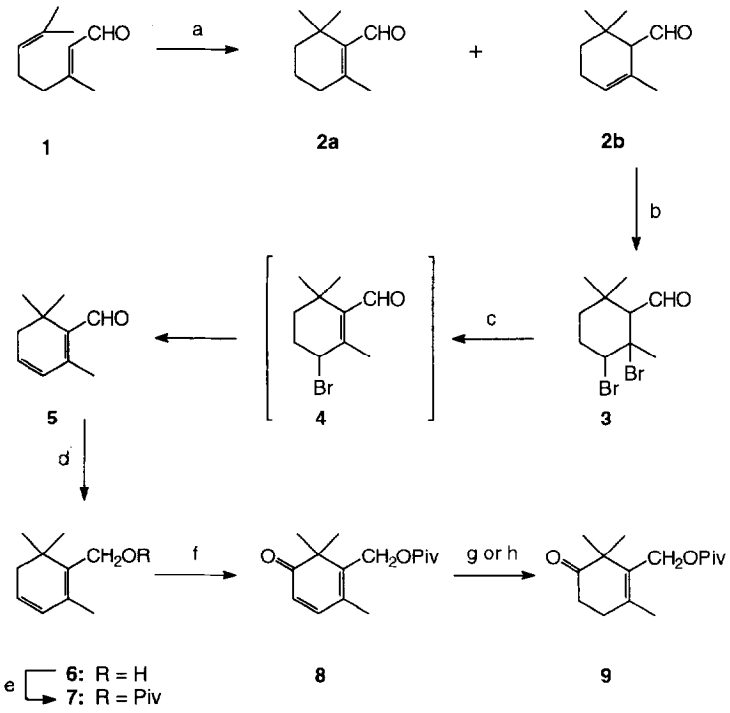
Scheme 1

RESULTS AND DISCUSSION

Safranal **5**,[9] the major constituent of saffron oil,[10] was envisioned to be ideally suited for the preparation of the A-ring building block for the synthesis of taxoids (Scheme 2). Safranal can also be prepared from the inexpensive citral in two or three steps. We reasoned that reduction of the aldehyde function of **5** followed by protection as the pivalate would give the conjugated allylic pivalate **7** which after allylic oxidation, and 1,4-reduction would furnish the desired ketone **9**, a possible taxol A-ring building block.

Treatment of a mixture of *E*- and *Z*-citrals **1** (Lancaster Synthesis) with aniline gave the corresponding Schiff bases[11] which were subjected to cyclization without purification in 95% sulfuric acid at -20 °C under argon to give a ca. 15:1 mixture of α- and β-cyclocitrals (**2b** and **2a,** respectively) in 48-55 % yield after distillation.[12] Using a minor modification of literature procedures,[13-15] this mixture was transformed to safranal **9** by bromination of the mixture of cyclocitrals in dichloromethane to the dibromide **3** followed by a two stage dehydrobromination with lithium carbonate in DMF. The carbonate was added in portions to the solution of the dibromide **3** in DMF (1 hr, rt) to give the allylic bromide **4**. Heating the solution at 100-110°C overnight gave safranal in 72 % yield.

The next step was chemoselective reduction of the conjugated aldehyde to the corresponding allylic alcohol. Of the various reducing agents examined, $NaBH_4/CeCl_3$ in aqueous ethanol at -15 °C[16] was the best one giving the known unstable alcohol **6**[17] in high yield. The crude alcohol was transformed without purification to the pivalate **7** (PivCl, py, CH_2Cl_2) in 92% yield over two steps.



REAGENTS: a) i) $PhNH_2$, $MgSO_4$, Et_2O, rt, 3 h; ii) conc H_2SO_4, -20...-30 °C, 48-55 %; b) Br_2, $CaCO_3$, CH_2Cl_2, -60 °C to rt; c) Li_2CO_3 , DMF 72 % from 15:1 mixture of **2b**:**2a**; d) $NaBH_4$, $CeCl_3$, EtOH:H_2O, - 15 °C; e) PivCl, pyr, CH_2Cl_2, 92 % over two steps; f) SeO_2; 37%, g) i) TMSCl, CuI, LiCl, Bu_3SnH, -60 °C to 0 °C; isolation of TMS-enolether of **9** ii) citric acid·H_2O/MeOH, 45 % from **8**, h) i) TMSCl, CuI, LiCl, Bu_3SnH, -60 °C to 0 °C; hydrolysis; then chromatography, 67%.

Scheme 2

Having the allylic pivalate **7** at hand we then turned our attention to the allylic oxidation. Of the several methods tried[18] selenium dioxide oxidation in refluxing dioxane[19] was the best one giving the desired enone **8** in 37 % yield. Attempted reduction of the enone by catalytic hydrogenation (5 % Pd/C or 5 % $Pd/BaSO_4$) to furnish the ketone **9** was unsuccesful yielding either starting material or overreduction products.[20] The desired 1,4-reduction was finally accomplished by copper hydride.[21] The desired ketone **9** was obtained in pure form in 45 % yield when isolated as the corresponding TMS-enolether by chromatography, followed by acidic

cleavage of the silyl group. When the TMS-enolether is hydrolysed during the aqueous work-up the ketone **9** was obtained in 67 % yield after repeated flash chromatography (hexane/MTBE).

CONCLUSIONS

The route presented gives a viable A-ring building block in only seven chemical steps starting from inexpensive citral or four steps from safranal. Considering the shortness and simplicity of this route we feel that the present method compares favourably with other approaches for the A-ring building block.[22]

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EXPERIMENTAL

General procedures.

The solvents were dried over appropriate drying agents. Thin layer chromatography was performed on silica gel 60 F_{254} plates from Merck. Spots were visualized under UV light (254 nm) and by spraying either with a 3 % vanillin ethanol solution containing 1 % H_2SO_4 or with a 1 % phosphomolybdic acid ethanol solution followed by heating with heat gun. For flash chromatography silica gel 60 (particle size 0.040-0.063 mm) from Merck was used. NMR spectra were recorded on a Bruker AM200 spectrometer.

Preparation of compound 7

To a stirred solution of safranal (0.504 g, 3.36 mmol) in ethanol (20 ml) at -15°C, water (34 ml) and $CeCl_3 \cdot 7H_2O$ (1.252 g, 3.36 mmol) were added. After 5-10 min sodium borohydride (0.190 g, 5.04 mmol) was added in one lot and stirring was continued until TLC showed that the starting material was consumed (16 min). Acetone (10 ml) was added and stirring was continued for another 5 min. Brine (50 ml) and ether (50 ml) were then added and the phases were separated and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated and the residue dissolved in methylene chloride and dried again with sodium sulfate. Evaporation of the solvent gave 0.489 g of compound **6** as pale yellow oil which was used immediately in the next step without further purification. The crude product (0.489 g) was dissolved in methylene chloride (5 ml), pyridine (5 ml) was then added and the solution was stirred under argon at 0°C. Pivaloyl chloride (410 µl, 3.31 mmol) was added dropwise and the mixture was stirred overnight, during which time the bath warmed to rt. The solvents were concentrated on a rotary evaporator ($t_{bath} \approx 30$°C) and toluene was added and evaporation was repeated. This was done twice. The product was purified by flash chromatography to yield 0.732 g (92%) of compound **7**.

Alcohol **6**: ^{1}H NMR ($CDCl_3$): δ 5.77 (2H, m), 4.25 (2H,s), 2.09 (2H, d, J = 2 Hz), 1.84 (3H, s), 1.29 (1H, br s, O<u>H</u>) 1.08 (6H, s). ^{13}C NMR ($CDCl_3$): δ 137.3, 129.2, 129.0, 126.1, 58.8, 39.9, 33.2, 26.5, 17.1. MS: 152 (M^+), 119 (100%). HRMS: found 152.1245 calcd for $C_{10}H_{16}O$ 152.1201.

Pivalate **7**: ^{1}H NMR ($CDCl_3$): δ 5.7-5.8 (2H, m), 4.68 (2H, s), 2.08 (2H, d, J = 2.2 Hz), 1.81 (3H, s), 1.21 (9H, s), 1.02 (6H, s). ^{13}C NMR ($CDCl_3$): δ 178.7, 132.5, 131.3, 129.1, 126.7, 61.2, 39.9, 38.8, 33.1, 27.2, 26.3, 18.1. MS: 236 (M^+), 119 (100%). HRMS: found 236.1747 calcd for $C_{15}H_{24}O_2$ 236.1776.

Preparation of Compound 8

Compound **7** (2.36 g, 10 mmol) was dissolved in dioxan (20 ml) under argon and freshly sublimed selenium dioxide (1.17 g, 10.5 mmol) was added and the mixture was refluxed for 30 minutes. The cooled mixture was poured on water and extracted four times with ether. The combined extracts were washed with water and dried over sodium sulfate. Filtration and concentration gave the crude product which was purified by flash chromatography on silica (eluent 9:1 to 2:1 hexanes/MTBE) to give 914 mg (37 %) of the desired enone **8**.

^{1}H NMR ($CDCl_3$): δ 6.92 (1H, d, J = 9.8 Hz), 6.09 (1H, d, J = 9.8 Hz), 4.71 (2H, s), 1.98 (3H, s), 1.22 (6H, s), 1.19 (9H, s). ^{13}C NMR ($CDCl_3$): δ 204.7, 177.9, 146.2, 144.2, 129.0, 124.9, 59.8, 48.8, 38.6, 26.9, 23.9, 18.1. MS: 250 (M^+), 57 (100%). HRMS: found 250.1551 calcd for $C_{15}H_{22}O_3$ 250.1569.

Preparation of Compound 9

Method A:

CuI (0.103 g, 0.543 mmol) and LiCl (54.2 mg, 1.28 mmol) were dissolved in dry THF (2.0 ml) under argon the solution was stirred at -55 °C to -60 °C. The enone **8** (53.3 mg, 0.213 mmol) was added in 1.5 ml THF followed by trimethylsilylchloride (145µl, 1.14 mmol) and the mixture was stirred for 10 min. Tributyltin hydride (161µl, 0.597 mmol) was added dropwise and the mixture was stirred for 130 min during which time the mixture was allowed to warm to 0°C. The mixture was treated with 10% aqueous KF (1.6 ml). After the gas evolution had ceased ether was added. The ether layer was filtered through Celite and the solvents were evaporated. The residue was stirred with 10% aqueous KF for 30 min. Extraction with ether washing with brine and drying over sodium sulfate gave the crude product which was purified by flash chromatography (9:1 hexanes/MTBE). The first fractions (42 mg) contained the desired compound as the trimethylsilyl enolether contaminated by a tributyltin compound. The later fractions gave 12 mg of 3:1 mixture (GC) of the desired ketone **9** and an impurity. The mixture of the TMS-enol ether and the tributyltin impurity was dissolved in methanol (2.5 ml), 62 mg of citric acid monohydrate was added, and the mixture was stirred for 5 hrs at room temperature. Evaporation of the solvent followed by flash chromatography gave 24 mg of pure ketone.

TMS-enol ether of **9**:

^{1}H NMR ($CDCl_3$): 4.68 (1H, t, J = 3.6 Hz), 4.60 (2H, s), 2.72 (2H, d, J = 3.4 Hz), 1.69 (3H, s), 1.19 (9H, s), 1.10 (6H, s), 0.21 (9H, s).^{13}C NMR ($CDCl_3$): 178.8, 154.6, 132.2, 130.7, 97.1, 60.8, 39.0, 38.8, 33.0, 27.2, 25.4, 18.8, 0.4. MS: 325 (M+1), 207 (100%). HRMS: found 324.2118, calcd for $C_{18}H_{32}SiO_3$ 324.2121.

Compound **9**: ^{1}H NMR ($CDCl_3$): δ 4.60 (2H, s), 2.44-2.59 (4H, m), 1.79 (3H, s), 1.19 (9H, s), 1.18 (6H, s). ^{13}C NMR ($CDCl_3$): δ 214.3, 178.6, 135.9, 131.7, 60.7, 47.0, 38.8, 35.6, 31.8, 27.1, 24.5, 19.5. MS: 252 (M^+), 57 (100%). HRMS found 252.1730 calcd. for $C_{15}H_{24}O_3$ 252.1725.

Method B:

The enone (0.4407g, 1.76 mmol) was allowed to react as above in the presence of CuI (0.855 g, 4.48 mmol) and LiCl (0.448 g, 10.56 mmol) with tributyltinhydride (1.33 ml, 4.93 mmol) and TMSCl (1.20 ml, 9.42 mmol) in THF between -60 and -50°C. When the reaction mixture warmed to +2°C brine was added and the mixture was stirred until gas evolution ceased. Extractive work-up with ether and water gave the crude product which was purified by flash chromatography (19:1 to 5:1 hexane/MTBE). Repeated purification gave a total of 0.2975g of ketone **9** (67 %) as a colourless oil.

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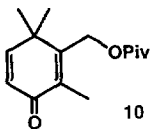
    Spectral data for compound **10**: ^{1}H NMR ($CDCl_3$): δ 6.81 (1H, d, J = 10 Hz), 6.25 (H, d, J = 10 Hz), 4.82 (2H, s), 1.94 (3H, s), 1.27 (6H, s), 1.20 (9H, s). ^{13}C NMR ($CDCl_3$): δ 186.1, 178.1, 156.9, 152.6, 136.3, 125.7, 60.2, 39.5, 38.8, 26.9, 25.0, 11.0. MS: 250 (M^+), 57 (100%). HRMS found 250.1575 calcd. for $C_{15}H_{22}O_3$ 250.1569.



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