Diastereoselective Synthesis of a *seco*-Taxane

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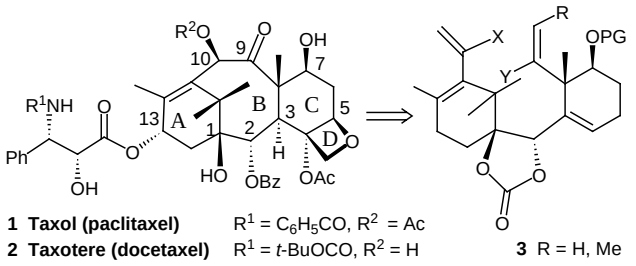
Abstract: Ketone **9** was synthesized in 7 steps from commercially available 2-methylcyclohexane-1,3-dione in a diastereoselective fashion.[1] Shapiro reaction of easily available trisylhydrazone **11** with benzaldehyde was used as a model for A- and C-ring coupling. Finally, reaction of trisylhydrazone **24** with A-ring aldehyde **4**, under carefully controlled conditions, gave *seco*-taxane **27** with high diastereoselectivity for the diol moiety.

Key words: Shapiro reaction, vinyllithium, stereoselectivity, seco-taxane, taxol

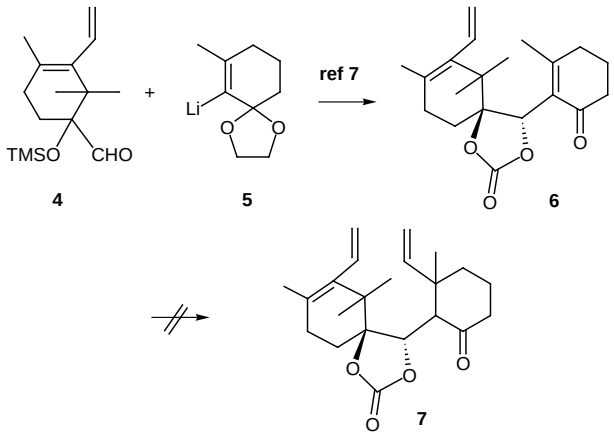
Due to their novel mode of action and complex structure as well as their low natural availability, taxol® **1**[2] and taxotere® **2**,[3] two potent antitumor agents, remain of great synthetic interest for organic chemists. At this time six total syntheses of taxol[4] and some synthetic approaches have been reported in several reviews.[5] Our convergent synthetic approach towards taxol is based on the preparation of the *seco*-taxane **3** by coupling A and C-rings. B-ring closure is envisaged from **3** through a metathesis reaction[6] or a vinyl-vinyl coupling reaction (Scheme 1).[7]



1 Taxol (paclitaxel) $R^1 = C_6H_5CO$, R^2 = Ac
2 Taxotere (docetaxel) R^1 = *t*-BuOCO, R^2 = H
3 R = H, Me

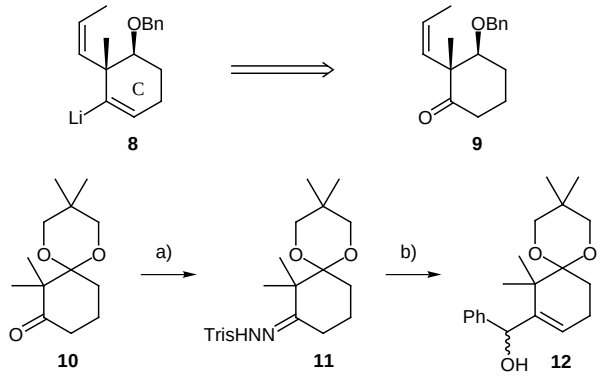
Scheme 1

In a first route, we synthesized compound **6** by coupling aldehyde **4** and vinyllithium derivative **5** derived from the corresponding vinyl bromide (Scheme 2).[8] To our surprise, this reaction was highly diastereoselective and delivered **6** as only one diastereomer (>95:5 by ^{1}H NMR) after protection of the diol system. Unfortunately, attempts to introduce the vinylic chain on the C-ring *via* conjugate additions of cuprates to enone derivative **6** failed to produce *seco*-taxane **7**.



Scheme 2

In order to get around the 1,4-addition at this stage of the synthesis, we decided to prepare a C-ring moiety encompassing the required vinylic function (Scheme 3). Vinyllithium intermediate **8** could arise from ketone **9** either directly under the Shapiro conditions[9] or *via* the corresponding bromide or iodide. To test the feasibility of the transformation from **9** to **8**, we used ketone **10** (which is an intermediate in the synthesis of **4**)[7] as a readily available model (Scheme 3). Trisylhydrazone **11** was obtained in 92% yield. When treated with 4 equivalents of *n*-BuLi, it furnished the vinylic anion which could be trapped with benzaldehyde to give **12** in good yield.



a) $TrisNHNH_2$, THF, HCl conc. cat., 92%. b) 4 equiv *n*-BuLi, THF/TMEDA 9:1, -78°C, 30 min, 0°C, 1 min, 4 equiv PhCHO, -78°C, 30 min, 77%.

Scheme 3

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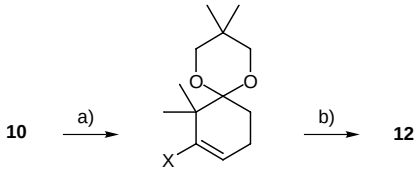
Vinyl bromide **13** and vinyl iodide **14** could not be obtained free of the corresponding alkene *via* trisylhydrazone **11**. However, formation of the unsubstituted hydrazone, followed by reaction with NBS[10] or iodine,[11] led to **13** or **14** in good yields and very cleanly (Scheme 4). Halogen-metal exchange was performed with *t*-BuLi and reaction of the vinyllithium derivative with benzaldehyde gave **12** in 90% and 51% yields respectively from **13** and **14**. In conclusion, all options to make vinyllithium derivatives **8** seemed to be open.



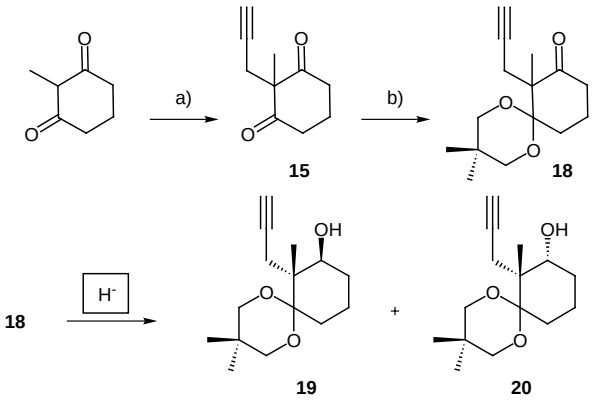
a) i- $H_2NNH_2.H_2O$, EtOH, Et_3N, 100°C, 12 h.; ii- NBS, Pyr, 0°C, 70% or I_2, DBU, Et_2O, 80%. b) 2 equiv *t*-BuLi, THF, -78°C, 30 min, 0°C, 1 min, 3 equiv PhCHO, -78°C, 30 min, 90% from **13**, 51% from **14**.

Scheme 4

We then addressed the preparation of ketone **9**. The baker's yeast mediated monoreduction of prochiral 2-methyl-2-propargylcyclohexan-1,3-dione **15**[12] has been described by Brooks,[13] yielding the hydroxyketone with the (2*R*,3*S*) configuration required for our synthesis. This procedure could be successfully reproduced with excellent ee (95%, determined by GC on the Mosher ester derivative), but the purification of the desired diastereomer proved difficult. In a first time, a racemic synthesis was effected.

Protection of ketone **15** as the monoketal **18** was not complete (60% yield, 40% starting material), but an easy separation *via* crystallisation of ketal **18** from the unpurified mixture allowed practical preparation of **18** in 75% yield after 3 turnovers. Diastereoselective reduction of the ketone function was then tested under several conditions (Scheme 5). Sodium borohydride reduction of **18** gave a 1:2 mixture of the two alcohols **19** and **20** in a quantitative yield, while Luche's conditions led to a 1:1 mixture of diastereomers. Reduction with DIBAl-H gave the undesired **20** as the major diastereomer, and L-Selectride led to a 4:96 ratio of **19**:**20**. Use of catalytic SmI_2/*i*-PrOH[14] led in this case to a poor conversion and a 1:1 ratio of isomers. The best yield was obtained with $LiAlH_4$ in toluene.[15]

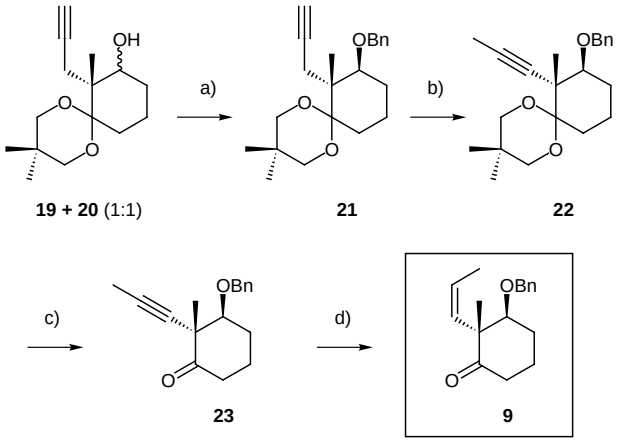
Alcohols **19** and **20** were not separated, and we took profit of a secondary reaction with the acetylenic group to protect selectively alcohol **19** as its benzyl derivative. Effectively, treatment of a 1:1 mixture of alcohols **19** and **20** with KH/THF/BnBr/cat. TBAI furnished benzyl derivative **21** as a pure isomer with concomitant degradation of alcohol **20** (Scheme 6). Having in hand the required pure compound **21**, treatment with *t*-BuOK led to an isomerization reaction of the acetylenic function and compound **22** was obtained in 88% yield. Acidic hydrolysis of **22** delivered the corresponding ketone **23** and partial hydrogenation of the triple bond afforded the expected ketone **9**.



Conditions	19 : 20
$NaBH_4$ /MeOH/CH_2Cl_2	1 : 2
$NaBH_4$/$CeCl_3$ /0°C	1 : 1
DIBAl-H/PhMe/ -78°C–>20°C	1 : 5
L-Selectride/THF/0°C	4 : 96
cat. SmI_2/*i*-PrOH/THF	1 : 1*
$LiAlH_4$/PhMe/60-70°C	53 : 47

a) NaH, DMF, propargyl bromide, 73%.
b) $HOCH_2CMe_2CH_2OH$, $BF_3.OEt_2$, CH_2Cl_2, 75%.
*15% conversion.

Scheme 5



a) KH, THF, BnBr, TBAI, 50%. b) *t*-BuOK, DMSO, 120°C, 88%. c) cat. TsOH, acetone, H_2O, >95%. d) H_2, Pd Lindlar >95%.

Scheme 6

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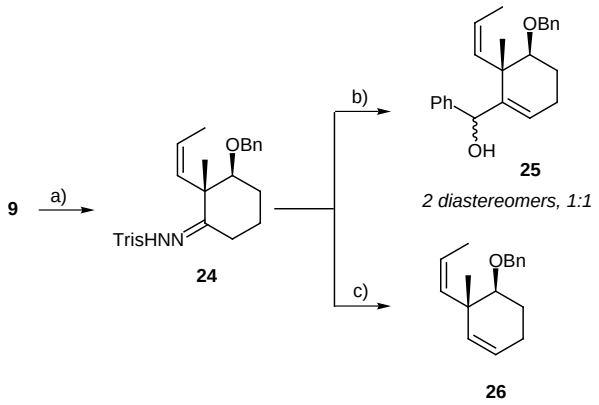
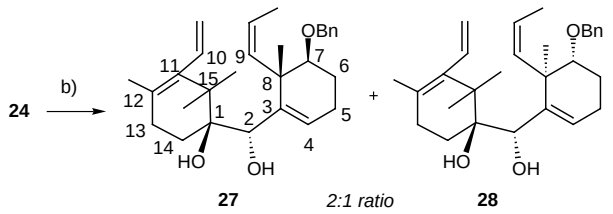
We then turned to the formation of the corresponding vinyllithium. Ketone **9** was converted to trisylhydrazone **24** in good yield, but attempts to make the unsubstituted hydrazone were unsuccessful: reduction of the terminal alkene was an unavoidable side-reaction. Under the previous Shapiro conditions (4 equiv *n*-BuLi, 9:1 THF/TMEDA, 4 equiv PhCHO), **24** led to adduct **25** in 65% yield (Scheme 7). But when A-ring **4** was used as the electrophile, with only 2 equiv of *n*-BuLi to avoid unwanted addition of the base onto the aldehyde, the reaction was not reproducible and yielded mostly alkene **26**, presumably because of a difficult formation of the vinylic anion.



a) TrisNHNH$_2$, THF, HCl conc. cat., 92%. b) 4 equiv *n*-BuLi, THF/TMEDA 9:1, -78°C, 30 min, 0°C, 1 min, 4 equiv PhCHO, -78°C, 30 min, 65%. c) 2.1 equiv *n*-BuLi, THF, -78°C, 30 min, 0°C, 1 min, 4, -78°C, 30 min.

Scheme 7

This problem was solved by using *t*-BuLi. After treatment of **24** with 2.2 equivalents of *t*-BuLi and addition of aldehyde **4**, the *seco*-taxane was obtained in 44% yield, after hydrolysis of the silyl ether with TFA, as a 2:1 mixture of diastereomers **27** and **28**,[16] but ^{1}H NMR analysis and nOe experiments showed clearly that the alkylation is totally stereoselective and only one diastereomer was obtained for the diol moiety (Scheme 8).[17]



a) i- 2.2 equiv *t*-BuLi, THF, -78°C, 30 min, 0°C, 1 min, 4, -78°C, 2 h, 44%; ii- TFA, CH_2Cl_2, 5 min, >95%.

Scheme 8

In conclusion, a new synthesis of a taxol C-ring was developed. The key coupling reaction of C-ring with A-ring using a vinyllithium intermediate was carried out via a Shapiro reaction. This reaction led to formation of seco-taxane 27 which possesses the required stereochemistry for taxol at the diol level. Preparation of an enantiopure seco-taxane is in progress, and B-ring closure using organometallic-catalyzed reactions will be tested in the near future.

Acknowledgement

The CNRS and the Ecole Polytechnique are thanked for financial support.

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(16) Typical procedure **9**–>**27**: To a solution of **9** (100 mg, 186 μmol) in 1.5 ml THF at -78°C was added dropwise over 3 min 260 μl (470 μmol, 2.5 equiv) of a 1.7 M *t*-BuLi solution in hexanes. The resulting red solution was stirred at -78°C for 30 min, during which time it turned to dark red. Temperature was then quickly raised to 0°C for 1 min, causing intense bubbling and decoloration to light yellow, then set back down to -78°C. A solution of aldehyde **4** (50 mg, 185 μmol) in 0.5 ml THF was then added *via* cannula to the vinyl anion solution prepared above, and the resulting mixture was stirred at -78°C for 2 h. The reaction mixture was quenched at -78°C by 2 ml of sat. aq. $NaHCO_3$ and allowed to warm to room temperature. The layers were separated, the aqueous layer was extracted with ether, and the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was diluted with 3 mL of CH_2Cl_2, treated with 10 drops of TFA and stirred at 20°C for 5 min. The reaction mixture was then concentrated *in vacuo* and the resulting crude product purified by flash chromatography on silica gel (eluant Et_2O/EP 20:80) to give 26 mg (30%) of **27** and 13 mg (14%) of **28** as colorless oils, along with 17 mg (34%) of recovered aldehyde **4** and 10 mg (22%) of alkene **26**.
27: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.37-7.25 (m, 5H, Ar), 6.20 (t, 1H, *J* = 3.8 Hz, H-4), 6.16 (brdd, 1H, *J* = 17.7, 11.2 Hz, H-10), 5.51 (dq, 1H, *J* = 12.2, 7.4 Hz, CH-9), 5.28 (dd, 1H, *J* = 11.1, 2.6 Hz, CH_2-10*cis*), 5.15 (dm, 1H, *J* = 12.2 Hz, H-9), 4.93 (dd, 1H, *J* = 17.6, 2.7 Hz, CH_2-10*trans*), 4.64 (d, 1H, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ar), 4.55 (d, 1H, *J* = 12.0 Hz, O-C$\underline{H}_2$-Ar), 4.27 (d, 1H, *J* = 5.6 Hz, H-2), 3.56 (dd, 1H, *J* = 11.3, 3.4 Hz, H-7), 2.77 (s, 1H, HO-1), 2.24-2.17 (m, 4H, CH_2), 2.03 (d, 1H, *J* = 5.8 Hz, HO-2), 1.94-1.86 (m, 2H, CH_2), 1.78 (dd, 3H, *J* = 7.5, 1.6 Hz, C$\underline{H}_3$-CH-9), 1.69 (s, 3H, CH_3-12), 1.72-1.47 (m, 2H, CH_2), 1.51, 1.21, 1.06 (3s, 9H, CH_3-8, CH_3-15); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm) 147.1 (Ar), 139.0 (3), 137.2 (11), 137.1, 135.9 (9, 10), 127.9, 127.2, 127.1, 126.0, 125.1 (Ar, 4, CH-9), 127.3 (12), 118.7 (CH_2-10), 82.2 (7), 76.2 (1), 71.8 (2), 71.4 (O-CH_2-Ar), 47.8 (8), 43.6 (15), 28.4, 27.6, 24.1, 22.5 (5, 6, 13, 14), 25.4, 22.4, 21.2, 14.6 (CH_3-8, CH_3-C-9, CH_3-12, 2 CH_3-15).
28: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.36-7.30 (m, 5H, Ar), 6.29 (dd, 1H, *J* = 5.4, 2.3 Hz, H-4), 6.18 (brdd, 1H, *J* = 17.4, 11.0 Hz, H-10), 5.53 (dq, 1H, *J* = 11.7, 7.1 Hz, CH-9), 5.46 (dm, 1H, *J* = 11.8 Hz, H-9), 5.28 (dd, 1H, *J* = 11.1, 2.7 Hz, CH_2-10*cis*), 4.93 (dd, 1H, *J* = 17.6, 2.7 Hz, CH_2-10*trans*), 4.62 (d, 1H, *J* = 12.0 Hz, O-CH_2-Ar), 4.53 (d, 1H, *J* = 12.0 Hz, O-CH_2-Ar), 4.19 (d, 1H, *J* = 4.5 Hz, H-2), 3.73 (dd, 1H, *J* = 11.7, 3.3 Hz, H-7), 2.90 (s, 1H, HO-1), 2.35-2.20 (m, 2H, CH_2), 2.10 (dddd, 1H, *J* = 18.4, 11.1, 5.6, 2.5 Hz, CH_2), 1.98 (d, 1H, *J* = 4.4 Hz, HO-2), 1.95-1.80 (m, 3H, CH_2), 1.70 (s, 3H, CH_3-12), 1.67 (d, 3H, *J* = 6.8 Hz, C$\underline{H}_3$-CH-9), 1.65-1.50 (m, 2H, CH_2), 1.22, 1.20, 1.10 (3s, 9H, CH_3-8, 2 CH_3-15); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm) 145.6 (Ar), 138.9 (3), 138.0, 135.9 (9, 10), 137.2 (11), 128.0, 127.4, 127.1, 126.2, 125.9 (Ar, 4, CH-9), 127.5 (12), 118.8 (CH_2-10), 81.1 (7), 78.7 (1), 71.6 (O-CH_2-Ar), 71.4 (2), 45.7 (8), 43.6 (15), 28.4, 27.6, 24.4, 23.6 (5, 6, 13, 14), 25.5, 22.3, 22.0, 21.1, 14.7 (CH_3-8, CH_3-C-9, CH_3-12, CH_3-15).

(17) A detailed analysis of diastereoselective additions of C-ring nucleophiles to A-ring aldehydes will be reported shortly.

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