Pergamon

Tetrahedron Letters 39 (1998) 279–282

TETRAHEDRON
LETTERS

"Abnormal" Eight-Membered Ring Formation through S_N2' Intramolecular Nozaki/Kishi Reaction in a Synthetic Approach to a Taxane Precursor

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Received 25 July 1997; accepted 28 October 1997

Abstract : Two different reactions were experimented for the construction of the eight-membered B-ring of taxane skeleton through the formation of the C9-C10 bond. A SmI_2 promoted radical reaction on *seco*-alkynyl aldehydes **11*cis*** or **11*trans*** failed. A Nozaki/Kishi reaction carried out on the *seco*-iodovinyl aldehyde **12*trans*** led, through an unprecedented intramolecular S_N2' reaction, to the "abnormally" cyclised product **14**, the structure of which has been confirmed by X-ray crystallography.

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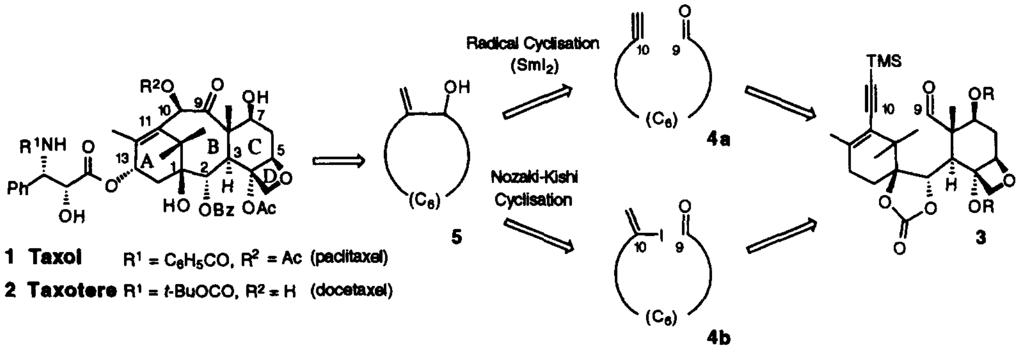
Our current efforts towards a total convergent synthesis of Taxol® **1** and Taxotere®[1] **2** led us to envision, as a final step for the construction of their tetracyclic skeleton, the formation of the C9-C10 bond from the convenient B-*seco*-taxane precursor **3**.[2] In parallel with the metathesis approach originally designed for executing this operation, it was decided to take advantage of the intermediate preparation of some interesting potential *seco*-precursors to test other cyclisation methods (**Scheme 1**). Either a radical samarium promoted reaction[3] from the acetylenic aldehyde **4a**, or a chromium catalyzed Nozaki/Kishi reaction[4] from the iodovinyl aldehyde **4b** could be envisaged as reasonable routes to the 8-membered B-ring of **1** or **2** *via* common cyclic α-methylene alcohols intermediates of type **5**.



Scheme 1

In this paper are reported the results of the cyclisation experiments carried out on the elaborated racemic aryl precursors **11** regarded as reasonable models for **3** (**Scheme 2**).

These models were easily prepared according to the straightforward route already developed for the synthesis of (±)*seco*-taxane model **6** that was obtained as an unseparable 2:1 mixture of *trans* and *cis* isomers[5] from condensation of the α-trimethylsilyloxy aldehyde **7** with *o*-lithiated styrene **9**.[6] Although in the presence of

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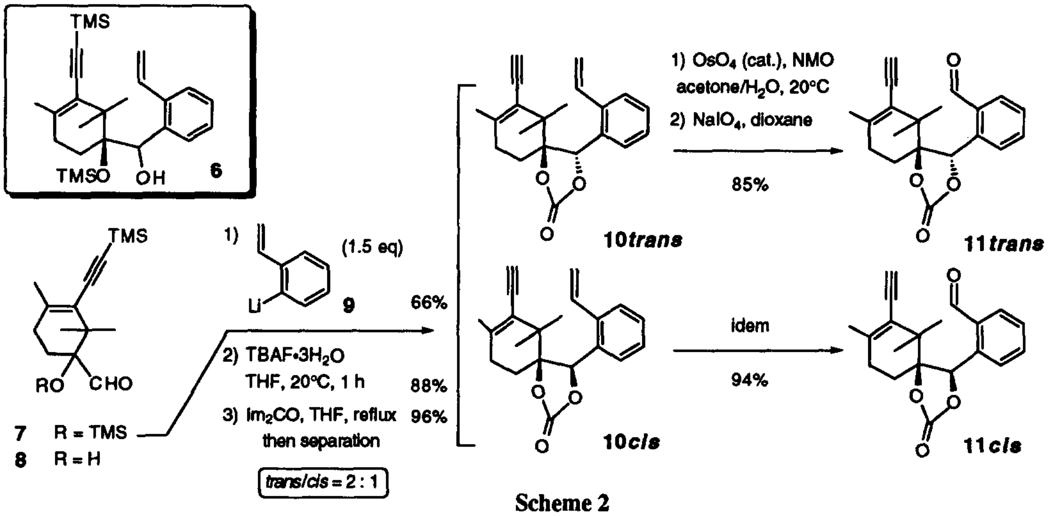
PII: S0040-4039(97)10512-3

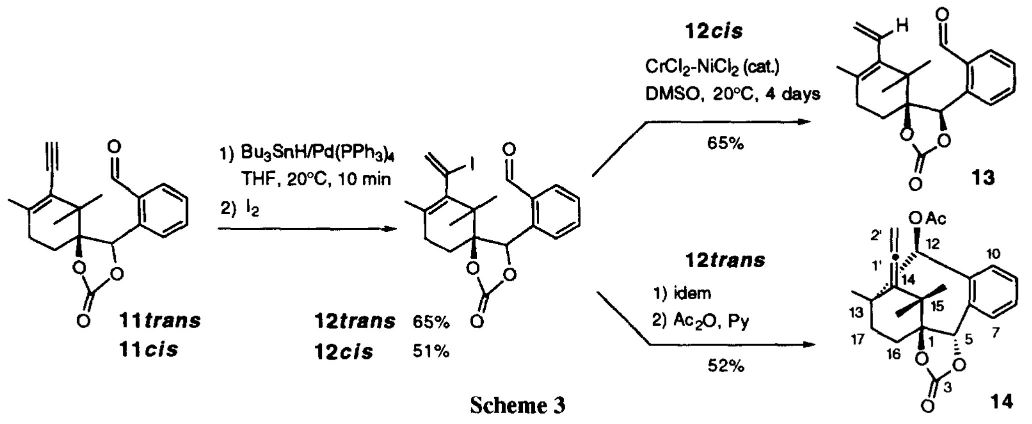
an excess of base, the pure natural *trans* isomer would be exclusively formed under chelate-controlled condensation of *o*-metallated styrene with α-hydroxy aldehyde **8**,[7] it was nevertheless decided to work on the less stereoselectively efficient α-trimethylsilyloxy aldehyde **7** in order to test, after subsequent separation, the cyclisation reactions on both 1,2-*trans* and 1,2-*cis* *seco*-precursors **11**. Therefore, the 3:2 mixture of *trans* and *cis* diastereomers obtained after condensation of **7** with **9** (66% yield) was successively treated with an excess of TBAF (88% yield), then with 1,1'-carbonyldiimidazole (96% yield) to give, after chromatographic separation, the pure carbonates **10*trans*** and **10*cis***. First attempts to prepare aldehydes **11** by ozonolysis of **10** failed: when **10*cis*** was ozonised (O_3, CH_2Cl_2/MeOH -78°C, then Me_2S) a new product was isolated in 38% yield and was shown to bear, beside the expected carbonyl group at C-9, an epoxide function at C11-C12. Such an epoxide formation during ozonolysis was already reported in the literature[8] and may be claimed to occur from oxidation of a spatially close second double bond by the hydroperoxide initially formed on the more reactive first double bond. Finally, an OsO_4 (cat.)/NMO-$NaIO_4$ oxidation sequence carried out on **10*trans*** or **10*cis*** afforded aldehydes **11*trans*** or **11*cis*** in 85% and 94% yield, respectively.



Scheme 2

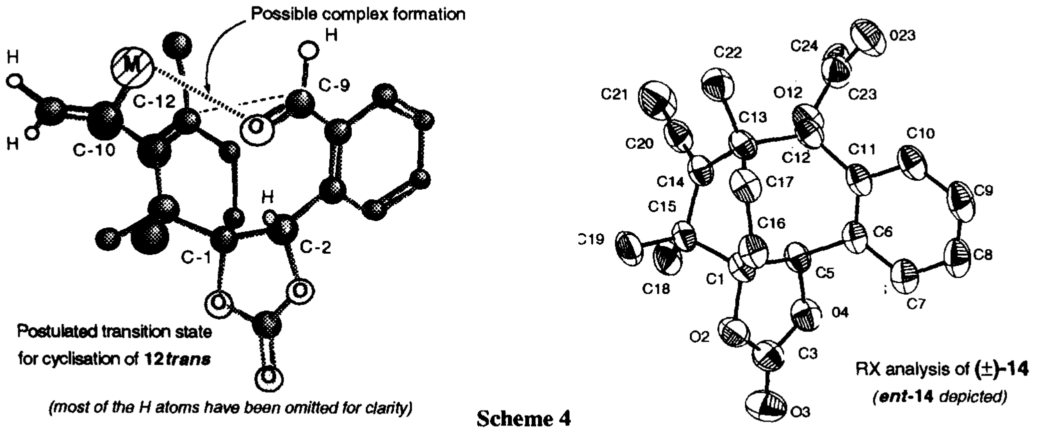
Having in hand the two alkynyl aldehydes **11*trans*** and **11*cis***, we then tried a first set of cyclisation reactions under SmI_2 radical conditions. When treated with SmI_2 (10 eq) THF as solvent and *t*-BuOH as a proton source (10 eq) no trace of the expected cyclic adducts was detected from their respective precursors (-78°C, 1-5 h, then rt, 15 h). From the complex reaction mixture, the only characterized products were the *seco*-alcohols resulting from reduction of the aldehyde function of **11**.

We next turned to the Nozaki/Kishi reaction (**Scheme 3**). The iodovinyl derivatives **12** required for the reaction were prepared in two steps. As expected from preceding studies,[9] Pd(0)-catalyzed hydrostannylation of both **11*trans*** or **11*cis*** only afforded the internal dienylstannanes with no trace of the distal regioisomers. Subsequent tin-iodine exchange[10] allowed isolation of the iodovinyl aldehydes **12*trans*** or **12*cis*** in 52% and 42% overall yields, respectively.[11] Subsequent treatment of aldehyde **12*cis*** with $CrCl_2$/$NiCl_2$ (cat.) in DMSO for 4 days at 20°C did not deliver any cyclized product but the diene **13** in 65% yield. This result clearly indicates that iodine-metal exchange occurred but the subsequent nucleophilic attack on the aldehyde function did not take place. Application of the same conditions to the iodovinyl aldehyde **12*trans*** gave, after subsequent esterification, the allene **14** in 52% yield.[12] Structure of **14** was established by ^1H NMR analysis including NOE experiments, and was finally secured by X-ray analysis.



Scheme 3

The reaction leading to **14** may result from addition of the allyl chromium intermediate formed from the vinyl iodide moiety onto the carbonyl function at C-9 according to an S_N2' mechanism. In our case, the favored "abnormal" cyclisation observed for **12*trans*** indicates that the C-9 and C-12 centers must be spatially close from each other as confirmed by molecular modeling (**Scheme 4**).[13] An oxygen-metal complexation may favor a chair-like six-membered transition state, a condition that could not be reached in the case of **12*cis*** due to angular distortions as well as non-bonding repulsive interactions between the *gem*-dimethyl group and the eclipsed aromatic ring (not depicted).



Scheme 4

Such a result is reminiscent of a Nicolaou precedent where reaction occurred at C-12 instead of C-10 in a $TiCl_3$-triggered attempt to cyclise a 9,10-dicarbonyl *seco*-precursor of taxol, leading to the major formation of a C9-C12 bond.[14] Intermolecular anionic examples of condensation of 2-metallo (Li, MgBr or Li/$CeCl_3$)-1,3-dienyl nucleophiles on ketones or aldehydes leading to β-hydroxyallenes were already reported,[15] but, to our knowledge, this is the first time that an intramolecular S_N2' Nozaki/Kishi reaction is described. Efforts are currently made to modify the structure of the precursors as well as to develop our initially programmed metathesis route to taxane skeleton.

Acknowledgments : The CNRS and the Ecole Polytechnique are thanked for financial support. We wish to thank Rhône-Poulenc S.A. Industry for a fellowship for B. M.

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11. ^1H NMR analysis of each the iodo-derivative **12*trans*** or**12*cis*** revealed that they exist as a 4:1 mixture of rotamers whereas their direct vinyltin precursors exist as a 1:1 mixture. The presence of such rotamers was confirmed by hydrodestannylation under acidic conditions of the latter vinyltin intermediates which gave, in each case, a single isomer.
12. Preparation of **14** : to a solution of $CrCl_2$ (85 mg, 0.7 mmol, 4.0 eq) and $NiCl_2$ (2.5 mg, 0.017 mmol, 0.1 eq) in degassed DMSO (10 mL) was slowly added *via cannula* solution of vinyl iodide **12*trans*** (80 mg, 0.177 mmol) in DMSO (16 mL). The resulting dark green mixture was stirred at 20°C for 7 days, then quenched by addition of a saturated aqueous NH_4Cl solution and diluted with diethyl ether. The aqueous phase was extracted with diethyl ether (x 3) and the combined organic phases were washed with water (x 3), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in pyridine (2 mL) and to this solution was added Ac_2O (85 mL, 0.89 mmol, 5 eq) and a few crystals of DMAP. The resulting mixture was stirred for 48 h at 20°C and quenched by addition of MeOH (1 mL). After evaporation of the solvent the crude residue was purified by chromatography on silica gel (diethyl ether/petroleum ether 5:95 to 40:60) to afford **14** (34 mg, 52%) as a white crystalline solid; mp 180-181°C. ^1H NMR (400 MHz, $CDCl_3$), NOESY experiment, δ 7.48-7.24 (m, 4H, H-arom), 5.87 (s, 1H, H-5), 5.69 (s, 1H, H-12), 4.96 (d, 1H, J = 10.8 Hz, Ha-2'), 4.88 (d, 1H, J = 10.8 Hz, Hb-2'), 1.99 (s, 3H, CH_3, $\underline{C}\underline{H}_3CO$), 1.85-1.68 (m, 2H), 1.41-1.31 (m, 1H), 1.31 (s, 6H, $2CH_3$, $2CH_3$-15), 1.28 (s, 3H, CH_3, CH_3-13), 1.06-0.99 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.2 (C-1'), 169.7 (CH_3-$\underline{C}O$), 154.1 (C-3), 136.7 (C-11), 134.7 (C-6), 133.8, 129.6, 128.5, 123.6 (C-arom), 110.3 (C-14), 90.6 (C-1), 82.0 (C-12), 79.9 (C-5), 79.1 (C-2'), 41.5 (C-15), 34.3 (CH_3, $\underline{C}H_3CO$), 29.8 (C-13), 28.9, 25.5 (C-16, C-17), 25.7, 21.8, 21.0 [$3CH_3$, CH_3-13 + $(CH_3)_2$-15].
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