Synthesis of the AC Ring of Paclitaxel: Formation of the C Ring by [3+2] Cycloaddition with a Preformed A Ring

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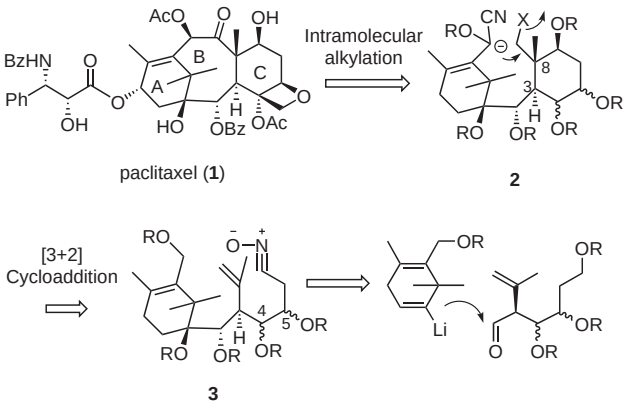
Abstract: The stereoselective formation of the C ring was accomplished by nitrile oxide [3+2] cycloaddition of an intermediate with the A ring already constructed. We found that stereoelectronic effect to a 1,1-substituted alkene moiety is important in the reaction.

Key words: paclitaxel, nitrile oxide, cycloadditions

Paclitaxel (**1**) is one of the most promising agents in cancer chemotherapy due to its strong antitumor activity.[1] Inspired by the potent biological activity, in addition to the synthetic challenges offered by the structure, our group has focused on the total synthesis of this natural product. We have already reported an efficient method for the construction of A, B, and C rings.[2–4] Based on these efforts, we now report the construction of the C ring using nitrile oxide cycloaddition reaction with a precursor containing the A ring.[5]

Our synthetic strategy to construct the ABC ring system of taxane is accomplished by way of intramolecular alkylation of the protected cyanohydrin ether **2**.[2] We previously developed methods to construct the A and C rings separately using a nitrile oxide [3+2] cycloaddition[3] and Ti-mediated radical cyclization.[4] However, from such precursors the preparation of the alkylation reaction precursor **2** is laborious. To overcome this difficulty, we planned the formation of the C ring using nitrile oxide cycloaddition reaction of intermediate **3**, with the A ring already constructed (Scheme 1).



Scheme 1 Synthetic strategy for paclitaxel.

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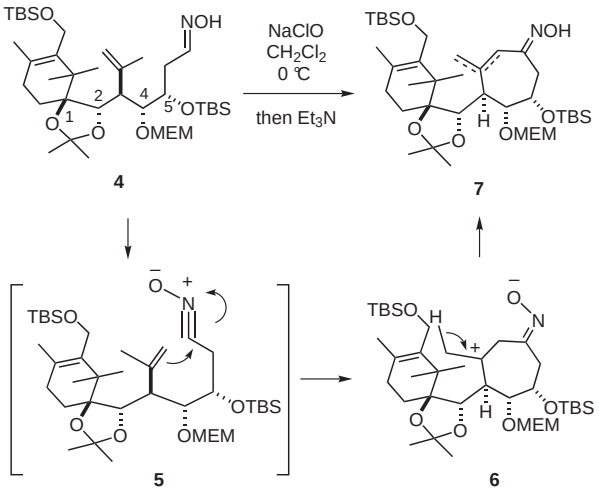
We have already demonstrated that modeling the nitrile oxide [3+2] cycloaddition based on the MM2 transition state models[6] is useful in predicting the product stereochemistry.[3,7] According to this established method, the effect of changing the stereochemistry at the C4 and C5 positions and protecting groups at the 4-hydroxy group in nitrile oxide **3** upon stereochemistry at the C8 position was investigated. These computational studies suggested that α-configuration of both alkoxy groups at the C4 and C5 position is preferable.

Based on this prediction, we initially prepared oxime **4** that has an acetonide for 1,2-diol and acyclic protecting groups for 4,5-diol. Treatment of oxime **4** with an aqueous solution of NaClO[8] and triethylamine at 0 °C provided nitrile oxide **5**, which underwent undesired 7-membered ring formation leading to **7** in 53% yield. The plausible mechanism is shown in Scheme 2. Cationic cyclization of **5** generates the favored tertiary carbocation **6** probably because the disubstituted alkene is too sterically hindered to undergo cycloaddition and/or more electron-rich than a monosubstitued alkene.[3b,9] Then, **6** undergoes β-proton elimination leading to **7**.[10]



Scheme 2

To avoid this cationic cyclization pathway, we next designed oximes **8**–**10**. MM2 transition state models suggested that **5** would adapt a boat-like transition state **A**, whereas the nitrile oxides derived from **8** and **9** could react by favorable chair-like transition states **B** and **C**, respectively, in order to undergo the desired [3+2] cycloaddition

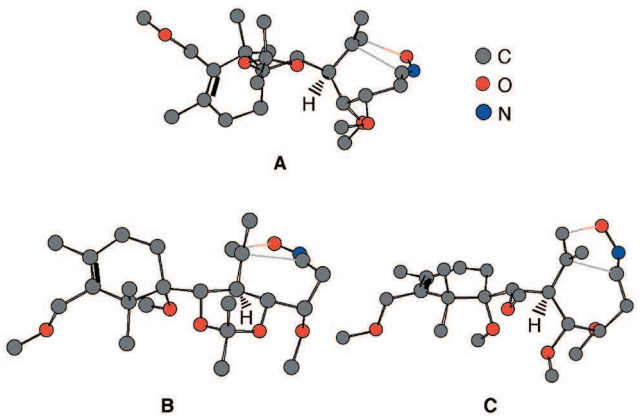
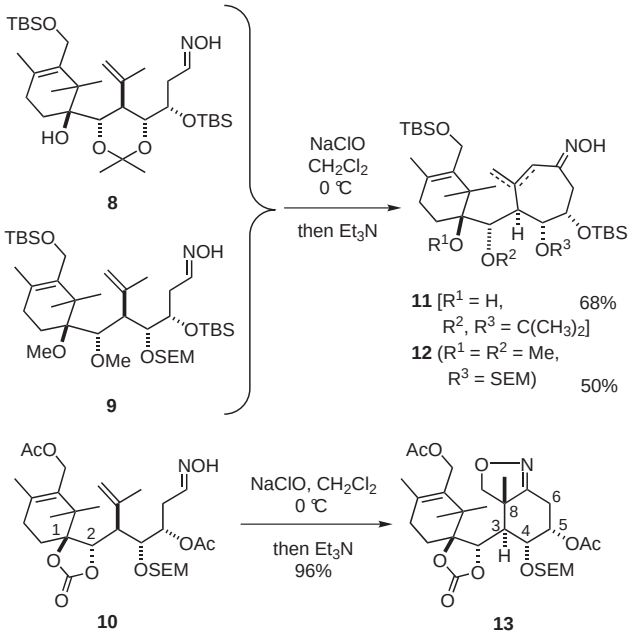


Figure 1 MM2 transition state models for nitrile oxide [3+2] cycloadditions from **5**, **8**, and **9**. Alkoxy groups were replaced by methoxy groups. Hydrogens are omitted in the drawing.

(Figure 1). In addition, we designed oxime **10** expecting the stereoelectronic effect of electron-withdrawing groups, i.e. 1,2-carbonate, to reduce electron density of the adjacent disubstituted alkene.

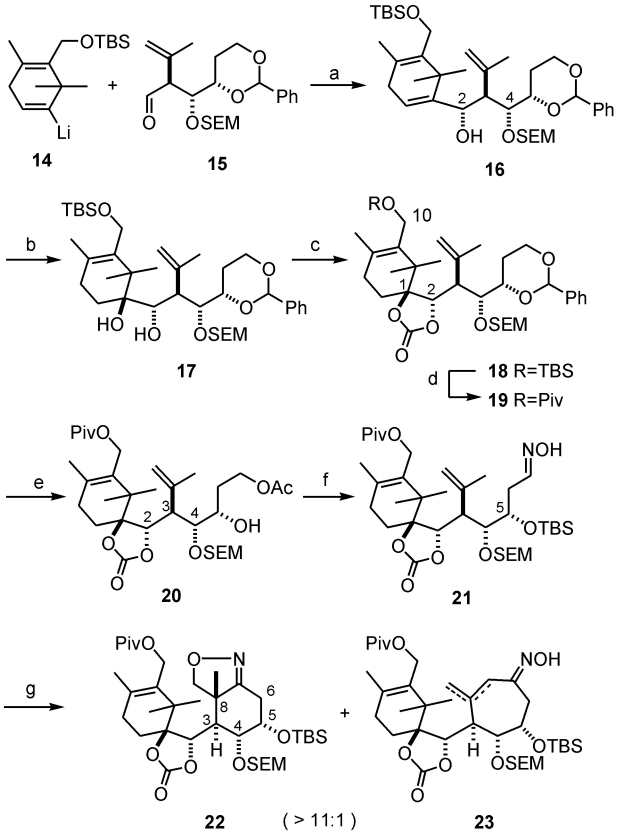
Cyclization of the nitrile oxides derived from oximes **8** and **9** gave the 7-membered ring products **11** and **12** in 68% and 50% yields, respectively (Scheme 3). Therefore, the ability to access a chair-like transition state did not affect the reaction pathway. The cycloaddition from oxime **10**, however, did proceed to provide the desired 6-membered ring product **13** in 96% yield with the desired stereochemistry. It should be noted that the stereoelectronic effect is important to control the reaction pathway in the cycloaddition. Based on this knowledge, we synthesized synthetically more useful intermediate **22** shown in Scheme 4.[11]



Scheme 3

Coupling of the A ring moiety **14**[12] and **15**[13] afforded the adduct **16** in 64% yield. The desired C2 α-hydroxy group[14] was a predominant product in a ratio of 80:20, and this result was explained by chelation control with the 4-OSEM group. Introduction of the C1 hydroxy group was carried out by epoxidation and reductive opening of the resulting epoxide. Selective protection of the partially deprotected allylic alcohol with TBS afforded **17**. Protection of diol **17** with a cyclic carbonate by exposure to triphosgene provided **18**. The TBS group on the A ring was converted to a Piv group. Removal of the benzylidene acetal in **19** under acidic conditions, followed by selective acetylation afforded **20**. Protection of the C5 alcohol with TBS, followed by removal of acetyl group, oxidation, and oxime formation furnished the cyclization precursor **21** in 54% overall yield.

The key [3+2] cycloaddition of **21** provided the desired 6-membered ring product **22** accompanied with a small amount of 7-membered ring product **23** (**22**:**23** = >11:1) in 95% combined yield.[15] The stereochemistry of **22** was determined based on the NOE observation shown in Figure 2.



Scheme 4 a) THF, –78 °C, 64%; b) i) TBHP, $VO(acac)_2$ PhH; ii) $LiAlH_4$, Et_2O, reflux; iii) TBSCl, imidazole, CH_2Cl_2, 3 steps 59%; c) triphosgene, pyridine, CH_2Cl_2, 93%; d) i) TBAF, THF; ii) PivCl, Et_3N, DMAP; e) i) CSA, MeOH; ii) Ac_2O, Et_3N, CH_2Cl_2, 4 steps 80%; f) i) TBSOTf, 2,6-lutidine, CH_2Cl_2; ii) K_2CO_3, MeOH; iii) TPAP, NMO, CH_2Cl_2; iv) $NH_2OH{\cdot}HCl$, pyridine, Et_2O, overall 54% (4 steps); g) NaClO, CH_2Cl_2, 0 °C; then Et_3N (95%).

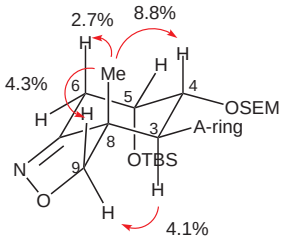


Figure 2 NOE observation of **22**.

In summary, we have demonstrated the [3+2] cycloaddition for the formation of the paclitaxel C ring in an advanced intermediate containing the A ring moiety. It is found that the stereoelectronic effect from the 1,2-cyclic carbonate controls the reaction pathway, favoring the desired [3+2] cycloaddition rather than cationic cyclization. Further study on the formation of the B ring toward the synthesis of paclitaxel is underway in our laboratory.

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(10) The structure of **7** was determined based on ^{1}H NMR and DEPT spectra.

(11) The β-elimination of the 5-acetoxy group in **13** disabled further transformation.

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(13) The aldehyde **15** was prepared as follows: (i) LDA, ethyl 3-methyl-2-butenoate; 2,4-*O*-benzylidene-2,4-dihydroxybutanal, 50% d.s., cf. ref.[3b]; (ii) $LiAlH_4$; (iii) TBSCl; (iv) SEMCl; (v) TBAF; (vi) TPAP, NMO.

(14) The stereochemistry was determined by the ^{1}H NMR coupling constants ($J_{2,3} = J_{3,4} = 10$ Hz) after acetonide formation for 2,4-diol from **17**.

(15) Spectral data of **22**: IR (neat): 2957, 1798, 1726, 1463, 1362, 1250, 1150, 1070, 837 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 9 H), 0.12 (s, 3 H), 0.15 (s, 3 H), 0.89 (s, 9 H), 0.86–0.97 (m, 2 H), 1.03 (s, 3 H), 1.11 (s, 3 H), 1.20 (s, 9 H), 1.33 (s, 3 H), 1.72 (s, 3 H), 2.00–2.17 (m, 2 H), 2.31–2.52 (m, 2 H), 2.43 (dd, 1 H, *J* = 1.93, 15.00 Hz), 2.69 (dd, 1 H, *J* = 2.90, 15.00 Hz), 2.87 (d, 1 H, *J* = 10.60 Hz), 3.55 (dt, 1 H, *J* = 6.28, 10.10 Hz), 3.60 (d, 1 H, *J* = 7.25 Hz), 3.74 (dt, 1 H, *J* = 6.28, 10.10 Hz), 3.77 (d, 1 H, *J* = 10.60 Hz), 4.15 (d, 1 H, *J* = 7.25 Hz), 4.32 (s, 1 H), 4.53–4.60 (m, 1 H), 4.56 (d, 1 H, *J* = 12.60 Hz), 4.60 (d, 1 H, *J* = 12.60 Hz), 4.70 (d, 1 H, *J* = 6.77 Hz), 4.81 (d, 1 H, *J* = 6.77 Hz). ^{13}C NMR (99.6 MHz, $CDCl_3$): δ = –4.5 (CH_3), –4.3 (CH_3), –1.3 (CH_3), 17.7 (CH_3), 18.2 (C), 18.3 (CH_2), 19.5 (CH_3), 24.0 (CH_2), 25.8 (CH_3), 25.9 (CH_3), 27.27 (CH_3), 27.35 (CH_3), 29.4 (CH_2), 29.6 (CH_2), 38.9 (C), 43.0 (C), 43.7 (CH), 56.0 (C), 61.1 (CH_2), 66.7 (CH_2), 68.6 (CH), 78.0 (CH), 80.9 (CH_2), 81.4 (CH), 88.7 (C), 96.5 (CH_2), 126.4 (C), 136.5 (C), 154.8 (C), 160.0 (C), 178.6 (C). ESI-TOF: *m*/*z* = 724.4 [M + H]$^+$.