Tetrahedron Letters 50 (2009) 3408–3410

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective one-pot three-component coupling approach towards the synthesis of the AC ring system of taxanes

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ARTICLE INFO

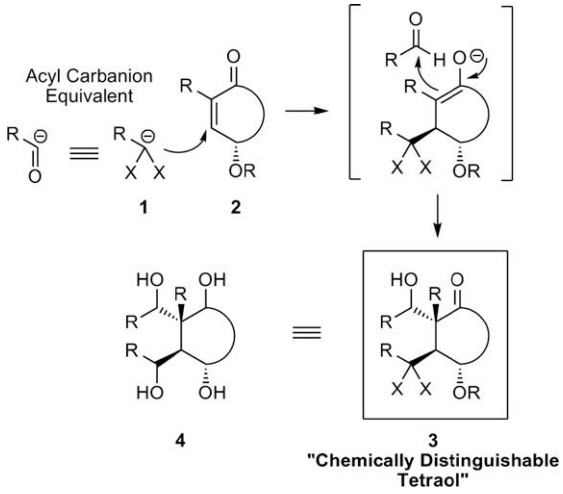
Article history:
Received 14 January 2009
Revised 14 February 2009
Accepted 19 February 2009
Available online 25 February 2009

ABSTRACT

The stereoselective one-pot three-component coupling reaction was accomplished by 1,4-addition of the protected cyanohydrin ether **9f** to cyclohexenone **10g** and subsequent addition of the resulting enolate to formaldehyde in high yield for the formation of the AC ring system of taxanes. We found that the bulky substituents at the 10-position in the A ring prevent the desired 1,4-addition. Similarly, the bulky trialkylsiloxy groups at the 4-position in the C ring prevent the 1,4-addition and electron-donating alkoxy groups at the same position induce the undesired retro-Michael reaction.

Stereoselective one-pot multi-component coupling reactions are very useful methods for constructing complex molecules from simple materials. The three-component coupling of an acyl carbanion equivalent **1** with a substituted cycloalkenone **2** and an aldehyde is especially powerful methods in natural product synthesis (Scheme 1). Because the highly functionalized coupling product **3** is regarded as an equivalent to the tetraol structure **4** which is found in a variety of natural products, such as paclitaxel, briarein A and illicinolide A.[1–3] This important structure can be stereoselectively synthesized from simple compounds in one-pot. The coupling product **3** is the 'chemically distinguishable tetraol'. The four oxygen functional groups in **3** are existed as a free alcohol, a protected alcohol, a ketone and a masked ketone. Therefore, those functional groups can be independently modified very easily. Protected cyanohydrin ethers are attractive as an acyl carbanion equivalent.[4] Because it has been reported that the anions of the cyanohydrin ethers preferentially undergo 1,4-addition to enones, whereas the dithian anions generally undergo 1,2-addition.[5–9] The protected cyanohydrin ethers are easily prepared from various aldehydes and are simply liberated by treatment with weak acid and diluted base. The successful applications of the one-pot three-component coupling reactions of the carbanions with the cyclopentenones and the various electrophiles for the natural product syntheses have been reported.[10–13] However, to the best of our knowledge, no study has been reported about three-component coupling of the acyl carbanion equivalents with cyclohexenones and aldehydes in one-pot. Here we wish to report the stereoselective one-pot three-component coupling reaction for the construction of the AC ring system of taxanes.

Paclitaxel **(5)** is one of the most potent, naturally occurring antitumour agents, and is widely used in cancer chemotherapy (Scheme 2). Inspired by the potent biological activity, in addition to the synthetic challenges offered by the structure,[14–19] our group has focused on the total synthesis of this natural product. We have already reported efficient methods for the construction of the A, B and C rings[20–23] and achieved a formal total synthesis of paclit-



Scheme 1. One-pot three-component coupling of acyl carbanion equivalents with cycloalkenones and aldehydes.

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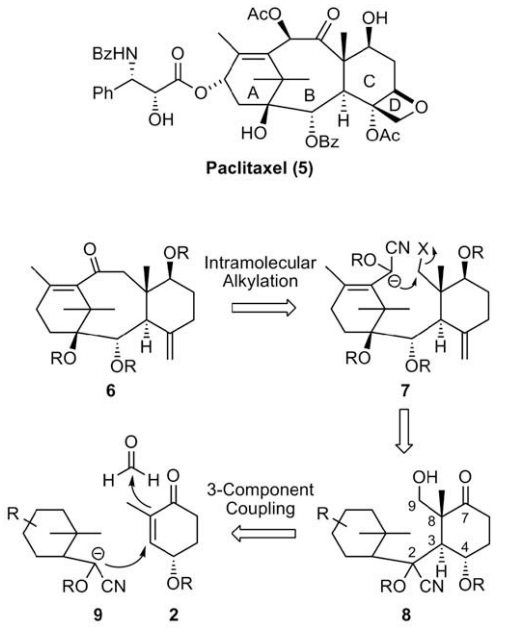
doi:10.1016/j.tetlet.2009.02.149

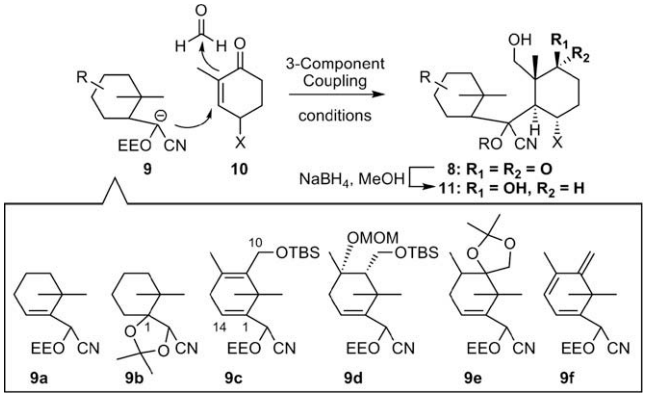


Scheme 2. Synthetic strategy for the ABC ring system of paclitaxel.

axel.[24] Our synthetic strategy to construct the ABC ring system of taxanes is shown in Scheme 2. We previously synthesized the AC ring **7** via the stereoselective anionic 1,2-addition of the A ring to the highly functionalized C ring.[22,24] However, the preparation of the highly functionalized C ring has been laborious in this case. To overcome this difficulty, we planned to use the one-pot three-component coupling reaction.[10–12,25] The functionalized AC ring **8** can be constructed by 1,4-addition of the protected cyanohydrin ether **9** to the 4-oxyfunctionalized cyclohexenone **2** and subsequent addition of the resulting enolate to formaldehyde. The coupling reaction could introduce the right trans stereochemistry between C(3) H and C(8) methyl. The key to success is how to suppress undesired retro-aldol and retro-Michael reactions because both reactions could be reversible.[26] In the coupling product **8**, the four oxygen functional groups exist as a ketone, a masked ketone, a free alcohol and a protected alcohol. Thus we can modify the oxygen functional groups at the 2-, 4-, 7- and 9-position independently towards the construction of **7**.

We initially prepared the protected cyanohydrin ethers **9a–f** to examine the effect of the substituents on the A ring (Table 1, entries 1–8). Treatment of **9a** with LiN(*i*-Pr)$_2$ in THF at −78 °C caused the 1,4-addition to 2-methyl-2-hexenone (**10a**) and the resulting enolate was coupled with formaldehyde to provide **8a** in 80% yield (entry 1). However, treatment of **9b** with base resulted in decomposition (entry 2). We assumed the instability of **9b** under basic conditions came from the oxygen functional group at the 1-position. Thus we designed **9c–f** that have $\Delta^{1(14)}$-alkene. Compounds **9c** and **9d** that have a bulky siloxy group at the 10-position gave unsatisfactory results (entries 3–5). On the other hand, the reaction of **9e** that has a cyclic acetal group at the 10-and 11-position produced desired coupling product **8e** in 68% yield when the carbanion formation and 1,4-addition were carried out at 0 °C (entry 7). It is envisioned that the bulky substituent at the 10-position prevents the 1,4-addition of the protected cyanohydrin ether to **10a**. Thus we designed **9f** that has no substituent at the 10-position. As expected, the coupling proceeded to furnish desired product **8f** in 90% yield (entry 8). Next we examined the effect of the substituents on the C ring (Table 1, entries 9–14). 4-Siloxy cycloalkenones **10e** and **10f** did not react with **9f** at all (entries 12 and 13). It is conceivable that the bulky siloxy groups on the C ring prevent the 1,4-addition of

Table 1
Three-component coupling reactions of the cyanohydrin ethers **9** with the substituted cyclohexenones **10** and formaldehyde



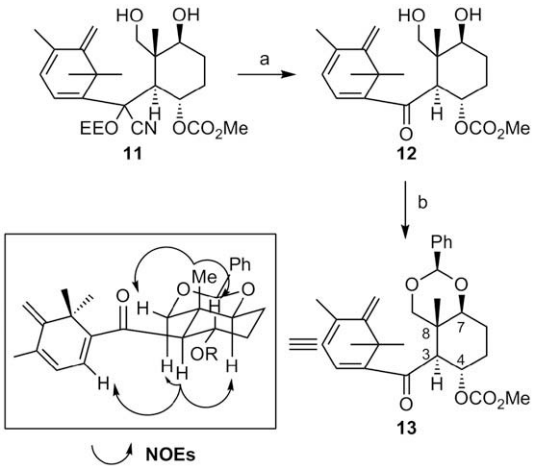
Entry	A ring	C ring	Conditions[a]	Yield (%)
1	**9a**	**10a** (X = H)	A	80 (**8a**)
2	**9b**	**10a** (X = H)	A	0 (**8b**)
3	**9c**	**10a** (X = H)	A	0 (**8c**)
4	**9d**	**10a** (X = H)	A	0 (**8d**)
5	**9d**	**10a** (X = H)	B	Trace (**8d**)
6	**9e**	**10a** (X = H)	A	Trace (**8e**)
7	**9e**	**10a** (X = H)	B	68 (**8e**)
8	**9f**	**10a** (X = H)	A	90 (**8f**)
9	**9f**	**10b** (X = OMOM)	A	Trace (**8g**)
10	**9f**	**10c** (X = OMEM)	A	Trace (**8h**)
11	**9f**	**10d** (X = OBOM)	A	Trace (**8i**)
12	**9f**	**10e** (X = OTMS)	A	0 (**8j**)
13	**9f**	**10f** (X = OTBS)	A	0 (**8k**)
14	**9f**	**10g** (X = OCO_2Me)	A	86[b] (**11**)

[a] Condition A: LiN(*i*-Pr)$_2$ (1.2 equiv), **9**, THF, −78 °C; **10**, THF, −78 °C; formaldehyde, THF, −78 °C. Condition B: LiN(*i*-Pr)$_2$ (1.2 equiv), **9**, THF, 0 °C; **10**, THF, 0 °C; formaldehyde, THF, −78 °C.
[b] Overall yield from **10g**.

9f. Interestingly, the enones **10b–d** had been consumed under the reaction conditions by TLC analyses. After the aqueous work-up, however, the enones were recovered without detection of the products in all cases (entries 9–11). Probably, the electron-donating alkoxy protecting groups, such as MOM, MEM and BOM, at the 4-position destabilize the 1,4-adduct to induce the retro-Michael reaction. Therefore, we designed **10g** that has a small electron-withdrawing carbonate group at the 4-position. As expected, neither retro-aldol nor retro-Michael reaction was observed and the desired three-component coupling product was obtained in high yield by TLC and NMR observations (entry 14). Subsequent stereoselective reduction of the ketone furnished diol **11** in 86% overall yield from **10g**.

Hydrolysis of the cyanohydrin ether provided the desired ketone **12** in 75% yield from **11** as a single diastereomer. The relative stereochemistry at the 3, 4-, 7- and 8-position was determined to be the desired configuration based on the NOE observation of benzylidene acetal **13**[27] derived from diol **12** (Scheme 3). This indicates that the 1,4-addition of the A ring occurs exclusively from the opposite side of the 4-alkoxy group. The subsequent addition of the enolate to formaldehyde proceeds stereoselectively from the opposite side of the protected cyanohydrin at the 3-position. Therefore, the desired product **12** would be obtained as a single diastereomer as expected.

In summary, the 1,4-addition of various cyanohydrin ethers **9a–f** to 2-methyl-2-cyclohexenone **(10a)** was investigated. Less hindered and highly conjugated **9f** was found to be the best Michael donor in this system and the subsequent aldol reaction with formaldehyde was accomplished in one-pot. Among the one-pot three-



Scheme 3. Determination of the relative stereochemistry at the 3-, 4-, 7- and 8-position. (a) (i) $CuSO_4$, $MeOH/H_2O$ (ii) 1 M NaOH aq, Et_2O, 2 steps 75%; (b) $PhCH(OMe)_2$, cat. CSA, CH_2Cl_2, 52%.

component coupling of **9f** with 4-oxyfunctionalized cyclohexenones **10b–g** and formaldehyde, the 4-(methoxycarbonyloxy)-2-methyl-2-cyclohexenone (**10g**) leads to the desired one-pot product in high yield, whereas the reaction of the enones **10b–d** having electron-donating alkoxy groups resulted in the observation of retro-Michael reaction of the products and the 4-(trialkylsiloxy)-enones **10e** and **10f** did not react at all. It should be noted that the carbonate protection at the 4-OH group suppresses the undesired retro-Michael reaction. Probably, the electron-withdrawing protecting group at the 4-position stabilize the 1,4-adduct. The obtained product **12** has the corresponding relative stereochemistry at the 3-, 7- and 8-position to paclitaxel. Moreover, all the four oxygen functional groups and the triene are very useful to construct the AC ring **7**. Further synthetic studies towards the ABC ring system of taxanes are underway in our laboratory and will be reported in due course.

Experimental procedure of the one-pot three-component coupling of **9f** with **10g** and formaldehyde. To a solution of *i*-Pr_2NH (0.398 mL, 2.99 mmol) in dry THF (5 mL) was added *n*-BuLi (1.82 mL, 1.57 M in hexane, 2.86 mmol) at 0 °C under argon. After being stirred at the same temperature for 30 min, a solution of the protected cyanohydrin ether **9f** (681 mg, 2.60 mmol, azeotropically dried with toluene) in dry THF (3 mL) was added dropwise at −78 °C over 20 min. After being stirred at the same temperature for 2 h, a solution of the cyclohexenone **10g** (240 mg, 1.30 mmol, azeotropically dried with toluene) in dry THF (1 mL) was added dropwise at −78 °C over 30 min. Then, the solution of the formaldehyde (30 mL, 0.5 M in THF, 15 mmol) was added in one portion at the same temperature. After being stirred for 5 min, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the crude ketone (1.20 g) in MeOH (10 mL) was added $NaBH_4$ (350 mg, 9.26 mmol) at 0 °C under argon. After being stirred at room temperature for 2 h, the reaction mixture was quenched by addition of 10% aqueous potassium sodium tartrate. The resultant mixture was stirred at room temperature for 1 h and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Silica, 60–70% EtOAc in hexane) to give the diol **11** (533 mg, 1.12 mmol, 86% from **10g**, diastereomixture) as a yellow solid.

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27. *Spectral data of* **13**: IR (neat): 2956, 1750, 1659, 1559, 1273, 1094 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.38 (s, 3H), 1.45 (s, 3H), 1.60–1.89 (m, 4H), 2.00 (br s, 3H), 3.15 (d, J = 10.9 Hz, 1H), 3.73 (s, 3H), 3.63–3.78 (m, 3H), 5.22 (d, J = 1.7 Hz, 1H), 5.25 (s, 1H), 5.22–5.34 (m, 1H), 5.50 (s, 1H), 5.92 (d, J = 6.3 Hz, 1H), 6.77 (d, J = 6.3 Hz, 1H), 7.33–7.47 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 12.5, 20.4, 25.2, 25.5, 28.6, 32.3, 37.8, 41.2, 52.6, 54.8, 73.8, 78.5, 83.0, 102.6, 111.9, 120.2, 126.2, 128.5, 129.2, 133.0, 138.0, 141.0, 146.8, 154.9, 155.2, 197.6.