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A Convergent Synthesis of Functionalized B-*seco* Taxane Skeletons

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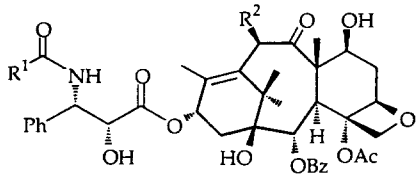
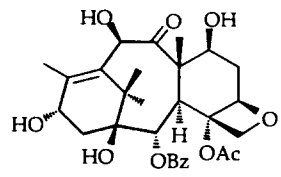
Abstract : The sequential Sonogashira cross-coupling reactions with water soluble and anhydrous Pd(0) catalysts between vinylic iodo derivatives **6**, **8** and 3-iodocyclohexenone **7** with trimethyl silyl acetylene are used to produce functionalized intermediates **11** and **18**. Conjugate addition followed by enolate trapping with trimethyl orthoformate provided B-*seco* taxane derivatives **14** and **20**.

The antitumor agents, paclitaxel (Taxol®) **1** and docetaxel (Taxotere®) **2** have generated much excitement due to their activities against advanced ovarian and breast cancer.[1] Taxol **1** has been the subject of extensive chemical and biological studies, which have been summarized in recent reviews.[1c,2] The recent total syntheses of taxol accomplished by Nicolaou[3] and Holton[4] are seminal achievements in the field.



1 : R^1 = Ph R^2 = OAc
2 : R^1 = OtBu R^2 = OH



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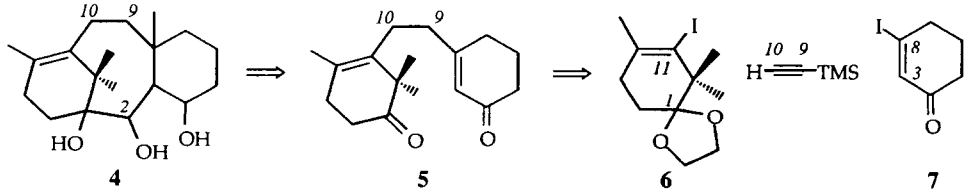
The challenge now is to provide new methodologies for the synthesis of 10-deacetylbaccatin III **3** [2b] analogues[5] which can rapidly lead to the analogues of taxol and taxotere.



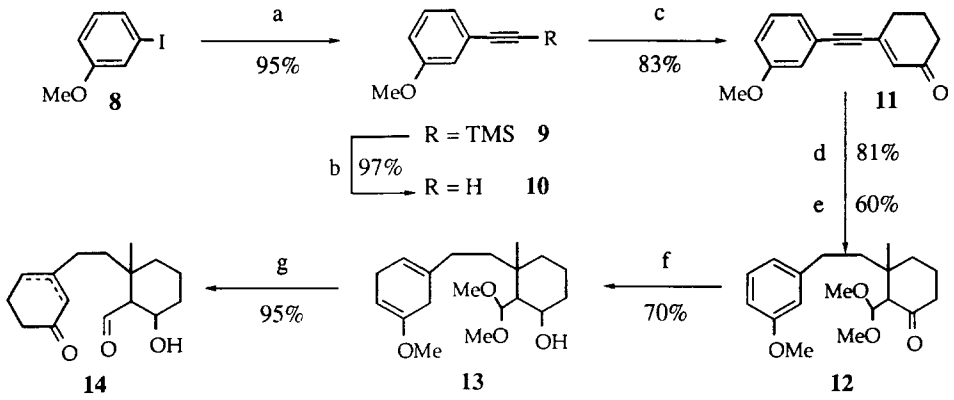
4 **5** **6** **7**

Scheme 1

We wish to report a convergent synthesis of B-*seco* taxane precursors of taxoids **4** by linking the future A and C rings through a two carbon moiety, via a sequential Sonogashira[6] reaction between the protected iodo-ketone **6** and 3-iodocyclohexenone **7** (Scheme 1).

The acetylenic moiety corresponds to the C-9 and C-10 of the taxane skeleton. The second step for the introduction of the methyl substituent at the C-8 involved a conjugate addition to the enone, followed by enolate trapping with trimethyl orthoformate to introduce the C-2 carbon atom.

In order to demonstrate the feasibility of this strategy, we started with 3-iodo anisole **8** as a simplified precursor of the A ring of taxol (scheme 2):



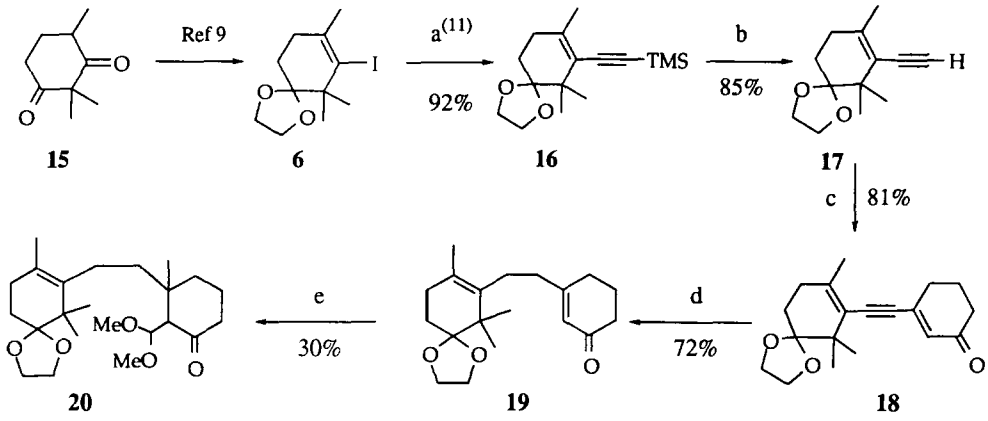
Reaction conditions : a) 5% $Pd(OAc)_2$, 10% TPPTS, 1.1eq TMSC≡CH, 2.5eq NEt_3, MeCN / H_2O, 40°C. b) 1.1eq TBAF, THF. c) 5% $Pd(OAc)_2$, 10% TPPTS, 2.5eq NEt_3, 3-iodocyclohexenone **7**, MeCN / H_2O, 40°C. d) 2eq H_2, 5% Pd/C, 10% Py, MeOH. e) 1.5eq Me_2CuLi, Et_2O, 0°C, then 7eq BF_3•Et_2O, 7eq $(MeO)_3CH$, -78°C, then NH_4Cl. f) 55eq Li, 70eq MeOH, THF, liq. NH_3, -78°C. g) Amberlist 15, acetone, H_2O.

Scheme 2

In the coupling step, reaction of trimethylsilylacetylene with the hydrosoluble palladium catalyst $Pd(OAc)_2$/ TPPTS without copper (I) promoter[6b] under the reaction condition shown in Scheme 2, afforded a 95% yield of **9**. Reaction of **9** with tetrabutylammonium fluoride in THF and treatment of the resulting acetylenic product **10** with 3-iodocyclohexenone using the conditions shown above led to the highly functionalized 3-substituted cyclohexenone **11**[7] in 83% yield. Hydrogenation of the triple bond and conjugate addition of Me_2CuLi (1.5 eq.) followed by trapping of the resulting enolate with trimethyl orthoformate led to **12**[8] in 70% yield. Birch reduction under controlled conditions (55 eq.Li, 70 eq. MeOH) afforded **13** which after hydrolysis gave **14** as a mixture of isomers.

We then turned our attention to the preparation of more elaborated B-*seco* taxane derivatives using our A+(C9-C10)+ C strategy. In this context the known 5,5-(ethylenedioxy)-2,6,6-trimethyl-1-iodocyclohexene **6**[9] prepared from **15**[10] was used as starting material.

Our synthesis of the B-*seco* taxane skeleton **20** is shown in scheme 3. Previously used aqueous conditions ($Pd(OAc)_2$/TPPTS, water-acetonitrile) failed to bring about the cross-coupling between **6** and trimethylsilylacetylene. Interestingly standard Sonogashira conditions afforded **16** in 92% yield,[11] which upon treatment with tetrabutylammonium fluoride in THF afforded **17**.



Reaction conditions : a) 40% PPh_3, 10% $Pd(OAc)_2$, 10% CuI, 6eq TMSC≡CH, 3eq NEt_3, THF, 80-90°C, 12h. b) 1.1eq TBAF, THF. c) 5% $Pd(OAc)_2$, 10% TPPTS, 3-iodocyclohexenone **7**, 2.5eq NEt_3, MeCN / H_2O, 40°C. d) 2eq H_2, 5% Pd/C, 10% Py, MeOH. e) 1.5eq Me_2CuLi, Et_2O, 0°C, then 7eq $BF_3.Et_2O$, 7eq $(MeO)_3CH$, -78°C.

Scheme 3

The cross-coupling of **17** with 3-iodocyclohexenone was carried out using $Pd(OAc)_2$/TPPTS in an aqueous medium,[6b] and **18** was obtained in good yield (81%). Complete hydrogenation of **18**[12] led to **19**.[13] Conjugate addition and enolate trapping under the reaction conditions shown in the Scheme 3 afforded the desired compound **20** in 30% overall yield (not optimized).

In summary, we have developed a facile and convergent synthesis of B-*seco* taxane skeleton utilizing sequential Sonogashira reaction. This method allows the rapid preparation of the valuable synthetic intermediates **19** and **20** which could be transformed into taxoid analogues via C-1,C-2 and C-2,C-3 ring closure. These studies as well as further works towards chiral derivatives are in progress.

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7 Spectral data for **11** : ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.94-2.06 (m, 2H, CH_2), 2.34-2.40 (m, 2H, CH_2), 2.41-2.44 (m, 2H, CH_2), 3.74 (s, 3H, OMe), 6.22 (t, 1H, ^{4}J=1.6Hz), 6.83-7.23 (m, 4H, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$), δ: 22.5, 30.4, 37.2, 55.2, 88.1, 99.5, 116.0, 116.5, 122.8, 124.4, 129.5, 132.4, 143.2, 159.3, 198.6; I.R. (film) (cm^{-1}): 2200, 1660, 1600; MS (m/z) : 226, 198, 170, 155, 127, 99, 77, 51.

8 Spectral data for **12** :^{1}H NMR (200 MHz, $CDCl_3$), δ: 0.96 (s, 3H, Me), 1.40-1.87 (m, 6H, CH_2), 2.10-2.60 (m, 5H), 3.23 (s, 3H, OMe), 3.25 (s, 3H, OMe), 3.69 (s, 3H, OMe), 4.65 (d, 1H, ^{3}J=7Hz), 6.60-6.71 and 7.04-7.55 (m, 4H, Ar); ^{13}C NMR (50.3 MHz, $CDCl_3$), δ: 21.9, 23.8, 29.6, 33.2, 39.8, 40.2, 41.6, 53.4, 55.0, 61.3, 102.5, 111.0, 114.0, 120.7, 129.2, 144.0, 159.6, 210.0; I.R.(film) (cm^{-1}): 1707, 1600, 1115; MS (m/z) : 320, 288, 256, 199, 121; Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22%; H, 8.81%. Found: C, 71.15%; H, 8.64%.

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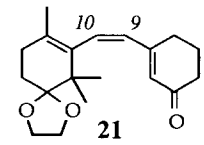
11 This high yield was obtained by running the reaction twice under the same conditions ($Pd(OAc)_2$, PPh_3, CuI, NEt_3, THF, sealed tube, 90°C) without intermediate purification. The product **16** was isolated as a colorless oil by flash chromatography (pentane, Et_2O 95/5). Spectral data for **16** :^{1}H NMR (200 MHz, $CDCl_3$), δ: 0.18 (s, 9H, $SiMe_3$), 1.16 (s, 6H, Me), 1.75 (t, 2H, ^{3}J=6.5 Hz), 1.90 (s, 3H, Me), 2.22 (t, 2H, ^{3}J=6.5 Hz), 3.97 (sl, 4H, OCH_2CH_2O); ^{13}C NMR (50.3 MHz, $CDCl_3$), δ: 0.7, 22.1, 23.2, 26.6, 30.3, 41.6, 65.0, 97.0, 103.5, 111.2, 123.6, 140.8; I.R. (film) (cm^{-1}): 2135, 1133; MS (m/z) : 278, 219, 192, 177, 86, 73; HRMS Calcd for $C_{16}H_{26}O_2Si$: 278.1702; Found: 278.1703.

12 The semi-hydrogenation of **18** is also possible affording the Z C9=C10 derivative **21** with a 43% non optimized yield. This compound could be useful in our strategy. Spectral data of **22** : ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.09 (s, 6H, Me), 1.55 (s, 3H, Me), 1.80 (t, 2H, ^{3}J=6.6 Hz), 1.95 (m, 2H), 2.18 (m, 2H), 2.38 (m, 2H), 2.46 (m, 2H), 3.99 (sl, 4H, OCH_2CH_2O), 6.01 (s, 1H), 6.17 (sl, 2H, CH=CH); ^{13}C NMR (50.3 MHz, $CDCl_3$), δ: 21.1, 23.0, 23.1, 26.5, 27.4, 30.4, 37.6, 42.6, 65.0, 111.6, 128.2, 128.9, 131.7, 134.9, 135.2, 159.3, 200.5; I.R. (film) (cm^{-1}) : 3052, 1651; MS (CI NH_3, m/z): 303.



21

13 Spectral data for **19** : ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.04 (s, 6H, Me), 1.69 (s, 3H, Me), 1.72 (t, 2H, ^{3}J=6,5Hz), 1.99-2.38 (m, 10H), 3.95 (sl, 4H, OCH_2CH_2O), 5.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ: 19.4, 22.6, 26.5, 26.6, 29.6, 30.4, 37.2, 38.2, 43.3, 64.8, 111.9, 125.0, 126.8, 135.0, 166.4, 199.8; MS (m/z) : 304, 218, 195, 86.

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