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Synthesis of a bicyclo[5.3.1]undecene by a facile domino enyne cross-metathesis/IMDA

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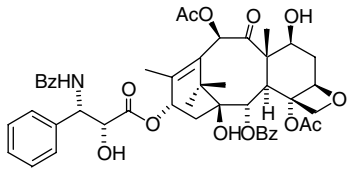
Abstract—An efficient domino cross-enyne metathesis/intramolecular Diels–Alder reaction is demonstrated for the construction of a bicyclo[5.3.1]undecene.

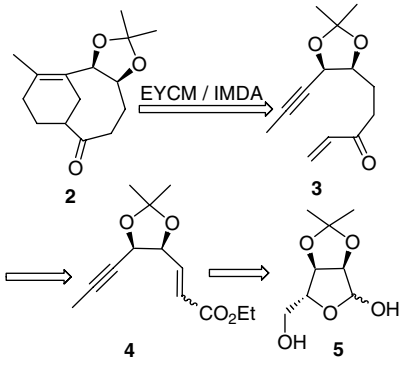
Bicyclo[5.3.1]undecene is a unique structural subunit present in many natural products, including Taxol™ **1**, which is an attractive synthetic target due to its outstanding biological activity and structural complexity.[1] Several innovative approaches have been developed to synthesize the core structure of Taxol, which has an unusual bicyclo[5.3.1]undecenone subunit.[2] Furthermore, six groups have successfully accomplished the total synthesis of Taxol[3–8] construction of the AB-ring moiety, consisting of a 10-membered ring bridged by one carbon, is still considered a difficult task.



1: Taxol (paclitaxel)

Tandem reactions are considered to be superior to stepwise procedures as several reactions can be combined in a single step and consequently a synthesis can be shortened significantly.[9] Among tandem reactions, the tandem enyne metathesis[10]/IMDA[11] reaction is particularly attractive because of its elegance in generating bicyclic rings with defined stereochemistry.[12] Though the domino intramolecular enyne metathesis/Diels–Alder reaction has been used extensively for the construction of bicyclic systems, its intermolecular counterpart (cross-enyne metathesis/IMDA reaction) has been less explored.[13] As a part of our chiron approach[14] towards the synthesis of biologically active compounds, we report here for the first time, a tandem enyne cross metathesis/IMDA strategy for the synthesis of bicyclo[5.3.1]undecenes.

There are several excellent contributions from various groups[15] for the synthesis of the AB-ring of Taxol via an intramolecular Diels–Alder reaction. We envisaged that a tandem enyne cross-metathesis/IMDA reaction could be an ideal key step for the construction of a bicyclo[5.3.1] undecene corresponding to the AB-ring of Taxol but without the *gem* dimethyl group. From a retrosynthetic perspective (Scheme 1), we considered the



Scheme 1. Retrosynthesis of the AB-ring system of Taxol.

Keywords: Taxol; Tandem; Enyne/cross-metathesis; IMDA; Chiron approach.
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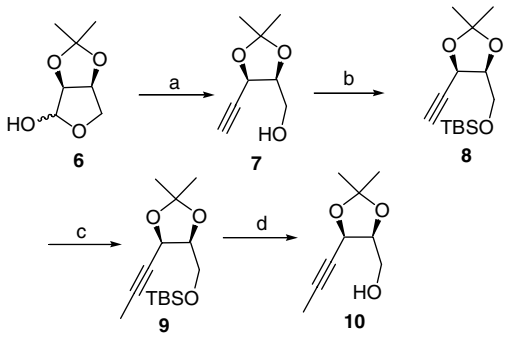
construction of **2** via, domino cross-enyne metathesis/IMDA reaction of enyne **3**. This acyclic ketone **3** could, in turn, be obtained from the unsaturated alkyne ester **4**. The ester **4** could then be derived from D-(+)-ribose monoacetonide **5** in a few steps.

Our synthetic sequence (Scheme 2) started with the known lactol **6**,[16] which was smoothly converted into the alkyne **7** by following the Ohiro–Bestmann protocol[17] in refluxing methanol in 76% yield. The primary alcohol **7** was then protected as its TBS ether **8** before treatment with *n*-BuLi and MeI to afford **9** in excellent yield. Removal of the TBS group was then easily achieved with TBAF to afford the alcohol **10** in 93% yield.

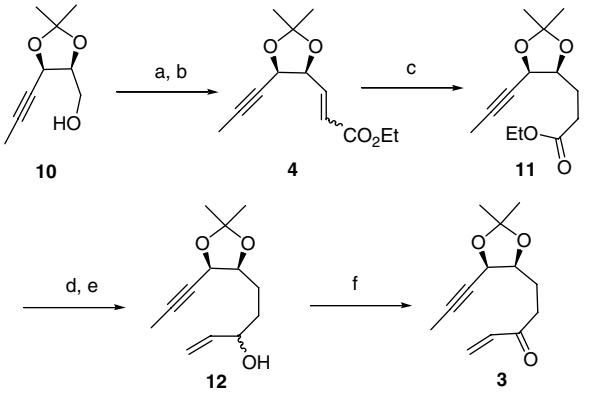
With alcohol **10** in our hand, our next task was to functionalize the right-hand side of the molecule to afford enyne **3**. We envisaged that alcohol **10** could be converted to the α,β-unsaturated ester **4**, which in turn could be reduced to furnish the saturated ester **11** thereby providing the desired extension of two carbon atoms.

Thus, the alcohol **10** was oxidized under Swern conditions, to provide an aldehyde, which was subsequently subjected to Wittig reaction to afford **4** in 60% yield over two steps (Scheme 3). Our next task was to reduce the double bond of enone **4** selectively in the presence of the alkyne. Unfortunately, conventional reduction methods such as Mg/MeOH,[18] $NiCl_2/NaBH_4$,[19] copper(I) hydride cluster $[(Ph_3P)CuH]_6$[20] and CuI/LAH[21] did not yield the desired product. Finally, we were relieved to find that Cu_2Cl_2 (0.75 equiv)/$NaBH_4$ (6 equiv) effectively reduced this unsaturated ester selectively at −20 °C to yield **11** in 80% yield.[22]

Subsequently, **11** was treated with DIBAL-H to afford the aldehyde which on treatment with vinyl magnesium bromide afforded a diastereomeric mixture of allylic alcohols **12** in 66% yield for two steps. The oxidation of allylic alcohol **12** with MnO_2 afforded the ketone **3** in 70% yield. The vinyl ketone **3** was found to be very unstable and polymerized quite rapidly even in the refrigerator. The synthesis of **3** set the stage for the tandem enyne/cross-metathesis/IMDA reaction.



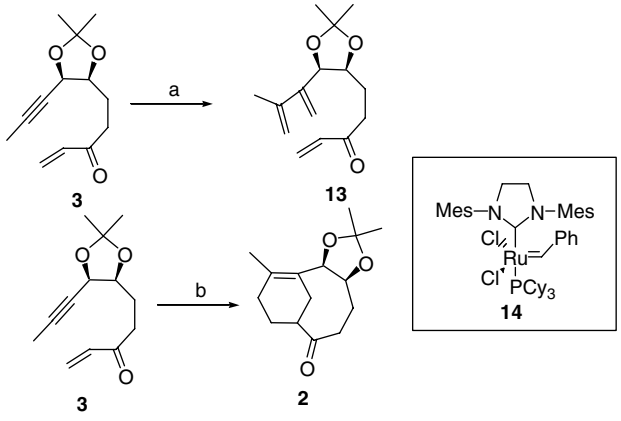
Scheme 2. Reagents and conditions: (a) dimethyl-1-diazo-2-oxopropyl-phosphonate, K_2CO_3, MeOH, reflux, 6 h, 76%; (b) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, rt, 2 h, 88%; (c) ^nBuLi, CH_3I, HMPA, THF, −78 °C to rt, 12 h, 96%; (d) TBAF, THF, rt, 2 h, 93%.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C, 1 h; (b) carboethoxymethylenetriphenyl phosphorane, CH_3CN, rt, 12 h, 60%; (c) Cu_2Cl_2, $NaBH_4$, THF, MeOH, −20 °C, 30 min 80%; (d) DIBAL-H, toluene, −78 °C, 30 min; (e) vinylmagnesium bromide, THF, −78 °C to rt, 12 h, 66%; (f) MnO_2, CH_2Cl_2, rt, 12 h, 70%.

When we carried out this reaction under 1 atm of ethylene in the presence of **14** in toluene at room temperature for 36 h (Scheme 4), we isolated the triene **13** in 86% yield based on 53% conversion.[23] We were hopeful that a domino cross enyne/IMDA reaction could be achieved if we performed the reaction at higher temperature, and indeed at 80 °C, we were delighted to see the enyne **3** underwent a smooth domino enyne metathesis/IMDA reaction to afford a single diastereomer of the bicyclo[5.3.1]undecanone **2** which corresponds to the AB-ring skeleton of Taxol without the *gem* dimethyl group in 62% yield.[24]

In conclusion, we have demonstrated a simple and straightforward tandem enyne cross-metathesis/IMDA reaction strategy, for the first time, to construct the bicyclo[5.3.1]undecene system. This structural subunit constitutes the AB-ring system of Taxol without the *gem* dimethyl group. In ongoing studies this strategy will be applied for the construction of the AB-ring of Taxol with appropriate functional groups present.



Scheme 4. Reagents and conditions: (a) **14** (10 mol %), ethylene, toluene, rt, 36 h, 86% based on 53% conversion. (b) **14** (10 mol %), ethylene, toluene, 80 °C, 48 h, 62%.

Acknowledgements

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24. All compounds reported here were fully characterized. Selected data: for **2**: $R_f = 0.44$ (2:8 ethyl acetate/petroleum ether); mp 98–100 °C; $[\alpha]_D^{25}$ −14.52 (*c* 0.57, $CHCl_3$); IR (KBr) ν_{max} 3352, 2921, 1701, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.14–4.05 (2H, m), 2.85 (2H, d, $J = 10.4$ Hz), 2.6 (1H, dt, $J = 11.6$, 3.2 Hz), 2.3–1.88 (6H, m), 1.81 (3H, s), 1.71–1.62 (2H, m), 1.45 (3H, s), 1.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.2, 145.5, 123.5, 107.9, 78.8, 78.3, 49.4, 36.7, 29.1, 27.4, 27.1, 27.0, 26.4, 19.3, 18.9; LRMS (EI) $[M+Na]^+$ 273.2426; HRMS (EI) calcd for $C_{15}H_{22}O_3Na$ *m*/*z* 273.1467, found *m*/*z* 273.1475. For **13**: $R_f = 0.58$ (2:8 ethyl acetate/petroleum ether); IR (neat) ν_{max} 2986, 1683, 1371, 1241, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.34–6.22 (1H, m), 6.33 (1H, d, $J = 10.4$ Hz), 5.85 (1H, d, $J = 10.4$ Hz), 5.41 (1H, s), 5.31 (1H, s), 5.19 (1H, s), 5.05 (1H, s), 4.45 (1H, d, $J = 8.4$ Hz), 3.8 (1H, dt, $J = 8.4$, 6.0 Hz), 2.9–2.7 (2H, m), 2.04–1.97 (1H, m), 1.94 (3H, s), 1.82–1.71 (1H, m), 1.46 (3H, s), 1.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 144.9, 141.7, 136.7, 128.4, 114.4, 114.1, 108.5, 80.9, 80.7, 36.2, 27.5, 27.2, 26.8, 22.3; HRMS (EI) calcd for $C_{15}H_{22}O_3Na$ *m*/*z* 273.1467, found *m*/*z* 273.1462. For **3**: $R_f = 0.6$ (2:8 ethyl acetate/petroleum ether); IR (neat) ν_{max} 2988, 2925, 2250, 1703, 1684, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.41–6.24 (1H, m), 6.35 (1H, d, $J = 10.4$ Hz), 5.86 (1H, d, $J = 10.4$ Hz), 4.21 (1H, d, $J = 8$ Hz), 3.95 (1H, dt, $J = 8$, 6 Hz), 2.87–2.7 (2H, m), 2.08–1.90 (1H, m), 1.86 (3H, d, $J = 1.2$ Hz), 1.88–1.73 (1H, m), 1.45 (3H, s), 1.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 136.5, 128.4, 109.6, 83.6, 80.7, 70.9, 70.3, 35.6, 27.2, 26.6, 25.9, 3.8; HRMS (EI) calcd for $C_{13}H_{18}O_3Na$ *m*/*z* 245.1154, found *m*/*z* 245.1148.