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Stereoselective synthesis of advanced intermediates en route to Taxuspine U and X: a study of macrocyclization via ring closing metathesis to highly constrained twelve-membered rings

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Dedicated to Professor Fulvio Gualtieri, University of Firenze, on the occasion of his 70th birthday

Abstract—The stereoselective synthesis of an advanced intermediate of Taxuspine U and X has been accomplished using a ring closing metathesis strategy. The feasibility of ring closing metathesis in synthesizing highly constrained and functionalized macrocycles has been demonstrated provided the appropriate substrate structure and substitution pattern are chosen.

Taxuspines U (**2**) and X (**3**) have been isolated from the stems of the Japanese yew *Taxus cuspidata*.[1] Taxuspines U (**2**) and X (**3**) are very rare bicyclic taxane-related diterpenoids and their skeleton has been proposed as a biogenetic precursor of taxanes[1c] (Fig. 1). Molecular modeling studies from our group have revealed that modified Taxuspines, such as **4** (Scheme 1) and analogs thereof, can adopt a conformation similar to the bioactive conformation of paclitaxel and can be well accommodated within the pseudoreceptor model proposed by us to predict the microtubule-stabilizing activity for taxanes.[2]

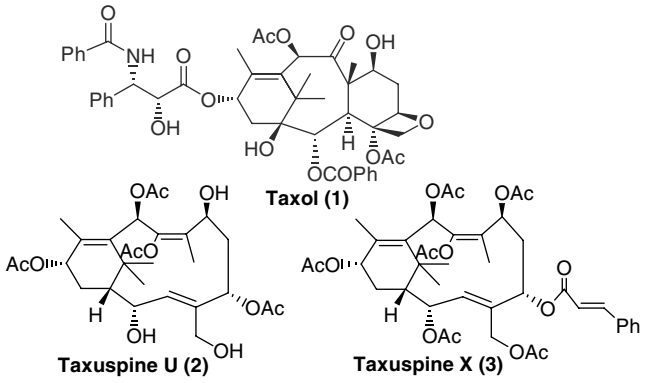

Figure 1.

Considering our recent work on the synthesis of Taxuspine U and X analogs via an original, convergent approach, involving a ring closing metathesis (RCM)[3] as a key step,[4] we focused our attention on the stereoselective synthesis of compound **5**, an advanced intermediate of Taxuspine U and X (Scheme 1). Our retrosynthetic analysis (Scheme 1) suggested that the twelve-membered macrocycle of **5** could be constructed by RCM of intermediate **6**, which is expected to result from the coupling reaction between the suitably functionalized alkyne **7**[4] and aldehyde **8**. In this letter, we describe the preparation of chiral synthon **8** using the SAMP/RAMP-hydrazones methodology,[5] the stereoselectivity of the alkynylation reaction, and our studies on the macrocyclization of substrate **6**.

The stereoselective synthesis of **8** is outlined in Scheme 2. 1,3-Dioxanone **9** has been obtained according to the procedure described in the literature[6] and transformed into the corresponding 2,2-dimethyl-1,3-dioxan-5-one-SAMP-hydrazone **10**. Smooth reaction of the azaenolate, generated by deprotonation with *tert*-buthyllithium at low temperature, with ethyl bromoacetate afforded ester **11** in a good yield. Cleavage of the chiral auxiliary by ozonolysis gave α-substituted ketone **12** in an

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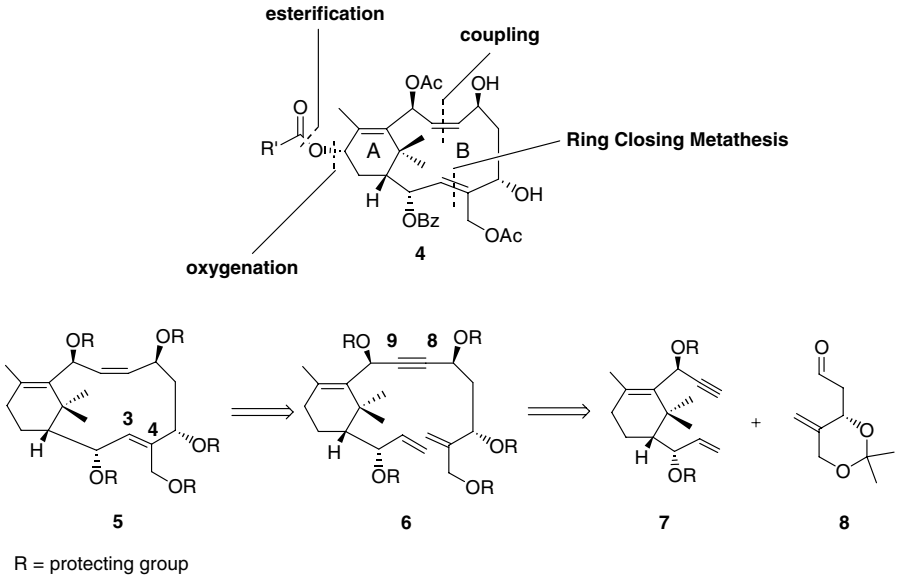
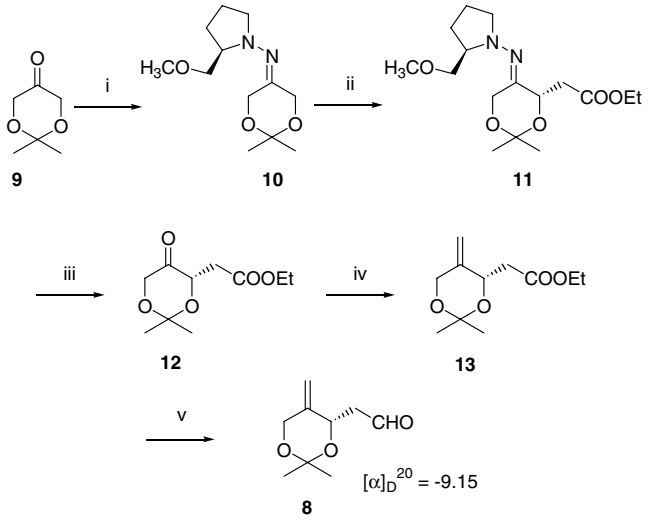
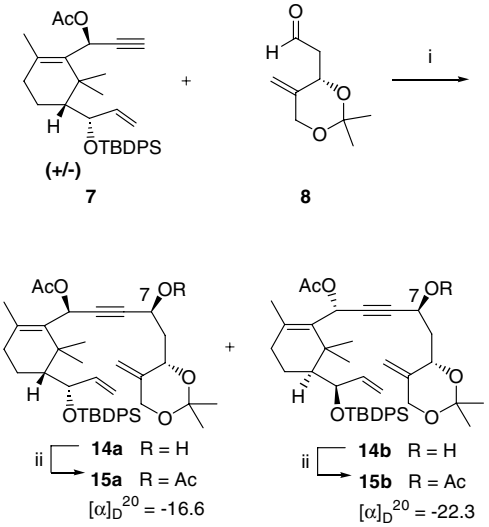


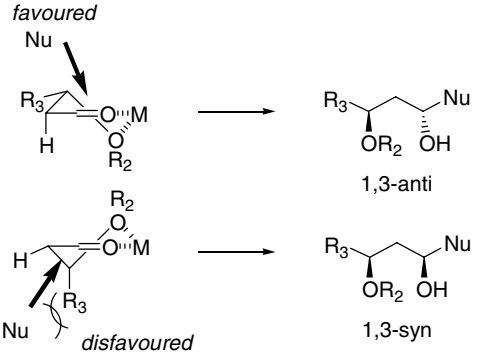
Scheme 1.



Scheme 2. Reagents and conditions: (i) SAMP, benzene, reflux, 12 h, 95%; (ii) *t*-BuLi, $BrCH_2COOEt$, THF, −78 °C to rt, 12 h, 75%; (iii) O_3, CH_2Cl_2, −78 °C, 4 h, 95%; (iv) $Ph_3P(Br)CH_3$, *t*-ButOK, THF, 0 °C to reflux, 1 h, 60%; (v) DIBAH, CH_2Cl_2, −78 °C, 30 min, 65%.



Scheme 3. Reagents and conditions: (i) LiHMSA, THF, −78 °C to rt, 1 h, 50–65%; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 95%.

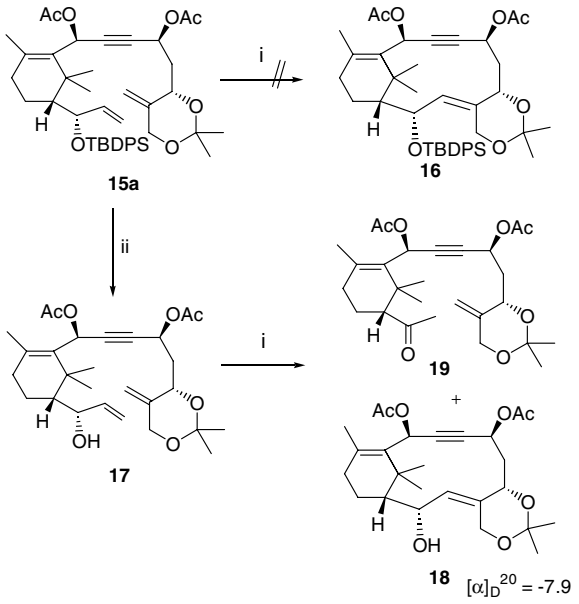


Scheme 4. Prechair transition-state model for bidentate 1,3-chelation.

excellent enantiomeric excess (ee = 89%, determined by HPLC with chiral column Chiralcel OD). Wittig olefination of the carbonyl moiety and partial reduction of the ester with DIBAH, led to the desired chiral aldehyde **8**.[7]

Reaction of the organolithium derivative of racemic alkyne **7** with the enantiomerically pure aldehyde **8** gave a 1:1 mixture of two diasteroisomeric alcohols **14a** and **14b** (Scheme 3).

The diastereoisomers have been separated by chromatography. HPLC/MS and NMR analysis on the O-acetylated compounds **15a**[8] and **15b** helped us in determining the relative stereochemistry of the newly formed stereocenter at C-7; COSY and NOESY experiments, performed at room and low temperature, revealed that the stereocenter at position 7 has the same configuration in both derivatives. The oxygen at



Scheme 5. Reagents and conditions: (i) RCM; (ii) TBAF, THF, 40 °C, 24 h, 80–95%.

the stereocenter in **8** plays a crucial role in controlling the stereochemistry of the reaction and our results are in agreement with the literature data concerning the alkynylation of chiral aldehydes.[9]

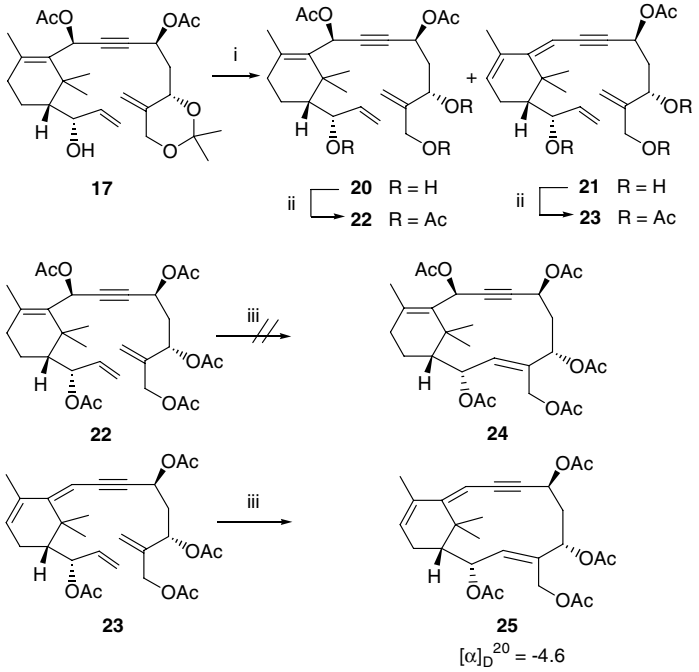
Due to the lithium chelation, in the prechair transition state (Scheme 4) the attack by the incoming nucleophile on the less hindered side of the aldehyde favors the formation of the 1,3-*anti* isomer, while the 1,3-*syn* reaction product is disfavored. Furthermore, thanks to this substrate-controlled reaction, the starting racemic mixture of alkyne **7** has been separated.

Several RCM assays have been performed on intermediates **15a** and **15b**, in the different conditions of solvent (CH_2Cl_2, $C_2H_4Cl_2$, toluene), dilution (1.0–3.5 mM), temperature (rt–60 °C), catalyst loading (10–20%), using both ruthenium (Grubbs I or Grubbs II catalyst) and molybdenum (Schrock catalyst) catalysts (Scheme 5). No case cyclization has been observed; the unaltered starting material has been recovered when the reactions have been run at room temperature, whereas degradation occurred at a higher temperature, in accordance with the outcome of the RCM reactions in our previous studies.[4]

It is known that RCM is strongly substrate-dependent mainly due to steric hindrance, complexation, and conformational preorganization of the acyclic dienic precursor;[10] therefore, ring closing metathesis reactions have been studied on modified substrates. After cleavage of silyl ether **15a**, the resulting less hindered allylic alcohol **17** was treated with 20% Grubbs II catalyst in refluxing dichloromethane; HPLC/MS analysis of the reaction mixture revealed the presence of the desired macrocycle **18** in 11% yield, whereas methyl ketone **19**[11] has been isolated as the major compound (Scheme 5). Competitive fragmentation reactions occur when the ring closure is slow[12] and it has been suggested that molecular strains in **17** favor this type of side reactions.

No improvement has been achieved when less hindered protecting groups for the allylic alcohol have been employed.

To enhance the flexibility of the acyclic precursor and to promote the approach of the terminal double bonds, the acetal functionality has been cleaved (Scheme 6) under acidic condition to afford the deprotected triol **20**,



Scheme 6. Reagents and conditions: (i) CH_3COOH 80%, 0 °C, 1 h; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 95%.; (iii) RCM.

together with the unexpected product **21** deriving from deacetylation and dehydratation at C-10 position. Although no other examples of this reaction have been described, we noticed that it occurs very easily in our C-13 unsubstituted substrates.

RCM on the O-acetylated derivative **22** proved to be unsuccessful, probably due to entropic reasons. Interestingly, when **23** was treated with 20% Schrock catalyst in toluene at 60 °C, bicyclic compound **25**[13] has been isolated in 23% yield. Based on molecular mechanics calculations, this result may be interpreted in terms of molecular constraints of **23**, which most likely create the appropriate distance and relative orientation for giving the ring closure between the two terminal double bonds.

In summary, we have applied the ring closing metathesis to synthesize highly constrained and functionalized macrocycles; so far, no example of twelve-membered carbocycle, obtained via RCM, has been reported in the literature prior to our studies.[4] Moreover, an original methodology to achieve the bicyclic core of Taxuspine U and X analogs has been developed. The reported study is part of a wider project aimed at designing and synthesizing new microtubule-stabilizing antimitotic compounds.

Acknowledgments

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References and notes

1. (a) Hosoyama, H.; Inubushi, A.; Katsui, T.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 13145; (b) Shigemori, H.; Wang, X.-X.; Yoshida, N.; Kobayashi, J. *Chem. Pharm. Bull.* **1997**, *45*, 1205; (c) Shigemori, H.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 245–256.
2. (a) Manetti, F.; Maccari, L.; Corelli, F.; Botta, M. *Curr. Top. Med. Chem.* **2004**, *4*, 203–217; (b) Maccari, L.; Manetti, F.; Corelli, F.; Botta, M. *Il Farmaco* **2003**, *58*, 659–668; (c) Wang, M.; Xia, X. Y.; Kim, Y.; Hwang, D.; Jansen, J. M.; Botta, M.; Liotta, D. C.; Snyder, J. P. *Org. Lett.* **1999**, *1*, 43–46.
3. For recent reviews see: (a) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (c) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830; (d) schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592–4633; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (f) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554; (g) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (h) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013–3043; (i) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565–588; (j) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211–240; (k) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (l) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (m) Blechert, S.; Schuster, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056; (n) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803; (o) Fürstner, A.; Langemann, K. *J. Org. Chem* **1996**, *61*, 3942–3943.
4. (a) Renzulli, M.; Rocheblave, L.; Avramova, S.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2004**, *45*, 5155–5158; (b) Renzulli, M. L.; Rocheblave, L.; Avramova, S. I.; Galletti, E.; Castagnolo, D.; Tafi, A.; Corelli, F.; Botta, M. *Tetrahedron* **2007**, *63*, 497–509.
5. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.
6. Enders, D.; Voith, M.; Iince, S. J. *Synthesis* **2002**, *12*, 1775.
7. Compound **8** has been characterized: IR (film): ν 1725, 1110 cm^{-1}. Electrospray MS *m/z* 203 $[M+Na]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ 9.8 (b, 1H), 4.83 (d, $J = 1.2$ Hz, 2H), 4.8 (m, 1H), 4.14 (dd, 1H, $J = 7.0$, 1.6 Hz), 2.77 (m, 2H), 1.55, 1.38 (2s, 6H). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.53; H, 8.30; $[\alpha]_D^{20}$ −9.15 (*c* 0.185, $CHCl_3$).
8. Compound **15a** has been characterized: Electrospray MS *m/z* 750 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.7–7.26 (m, 10H), 5.99 (s, 1H), 5.84 (ddd, 1H, $J = 18.0$, 10, 8.4 Hz), 5.65 (dd, 1H, $J = 9.7$, 3 Hz), 4.84 (d, 2H, $J = 7.5$ Hz), 4.61 (d, 1H, $J = 10$ Hz), 4.56 (d, 1H, $J = 17$ Hz,), 4.35 (d, 1H, $J = 8.7$ Hz), 4.38 (d, 1H, $J = 9.7$ Hz), 4.26 (s, 2H,), 2.27 (m, $1H_{6a}$), 2.2–2.0 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.94 (m, $1H_{6b}$), 1.87 (s, 3H), 1.65–1.4 (m, 2H), 1.36 (s, 3H), 1.35 (dd, 1H, $J = 10$, 3 Hz), 1.25 (s, 3H), 1.01 (s, 3H), 0.95 (s, 9H), 0.87 (s, 3H). Anal. Calcd for $C_{44}H_{58}O_7Si$: C, 72.69; H, 8.04. Found: C, 72.74; H, 8.02; $[\alpha]_D^{20}$ −16.6 (*c* 0.217, $CHCl_3$).
9. Guillame, S.; Plé, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355–2403.
10. (a) Van de Weghe, P.; Eustache, J.; Cossy, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1461–1472, and references cited therein; (b) Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473–1494; (c) Van de Weghe, P.; Eustache, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1495–1519.
11. Compound **19** has been characterized: Electrospray MS *m/z* 281, 497 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.59 (m, 1H), 4.84 (d, 2H, $J = 1.2$ Hz), 4.58 (m, 1H), 4.28 (m, 2H), 2.6–2.4 (br s, 1H), 2.15 (s, 3H), 2.0–1.6 (br s, 6H), 2.05, 2.04 (2 × s, 6H), 1.90 (s, 3H), 1.44, 1.38 (2 × s, 6H), 1.07 (s, 3H), 099 (s, 3H). Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.21.
12. (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880; (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125.
13. Compound **25** has been characterized: Electrospray MS *m/z* 509 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.02–5.89 (m, 3H), 5.42 (m, 1H), 5.29–5.24 (m, 1H), 5.21–5.17 (m, 1H), 4.46 (br s, 2H), 2.56–2.44 (m, 2H), 2.12 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.06–2.03 (m, 1H), 2.01 (s, 3H) 1.94 (s, 3H), 1.54, 1.43 (m, 2H), 1.26 (s, 3H), 1.16 (s, 3H). Anal. Calcd for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04. Found: C, 66.57; H, 7.06; $[\alpha]_D^{20}$ −4.6 (*c* 0.175, $CHCl_3$).