Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5155–5158
Tetrahedron Letters

Studies toward Taxuspine X, a potent multidrug-resistance reversing agent, via ring closing metathesis strategy

Michela L. Renzulli, Luc Rocheblave, Stanislava Avramova, Federico Corelli and Maurizio Botta*

Dipartimanto Farmaco Chimico Tecnologico, Università degli Studi di Siena, via A. Moro snc, Siena 53100, Italy

Received 25 February 2004; revised 22 April 2004; accepted 23 April 2004

Dedicated to Professor R. Nicoletti on the occasion of his 70th birthday

Abstract—The synthesis of bicyclic 3,8-secotaxane diterpenoids, which includes Taxuspine U and X, has been achieved through an approach that involves a ring closing metathesis reaction as key step for the macrocycle formation.

The remarkable therapeutic importance and challenging structural complexity of taxane diterpenoids (Fig. 1) have stimulated worldwide enormous efforts. In spite of numerous synthetic approaches toward paclitaxel (Taxol®, **1**) and docetaxel (Taxotere®, **2**), including six total syntheses,[1] not enough attention has been paid on bicyclic 3,8-secotaxane diterpenoids, such as Taxuspine X (**3**) and U (**4**), whose bicyclic skeleton has been proposed as biogenetic precursor for taxanes.[2] Molecular modeling studies from our group have revealed that modified Taxuspines, such as **5** 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.[3,4] Moreover, Taxuspine X (**3**) exhibits remarkable multidrug-resistance (MDR)-reversing activity.[5] Due to these observations, compounds **5** can be reasonably envisaged as common precursors for the development, through appropriate chemical modifications, of either new anticancer drugs mimicking Taxol® or MDR reversing agents, such as Taxuspine X. Surprisingly, no total synthesis of Taxuspines has been reported so far, in the face of their interesting biological properties and thera-peutic potential. A few years ago our research group described its own distinctive approach to the synthesis of a bicycle[9.3.1]pentadecane skeleton based on the Dieckmann cyclization of a diester intermediate.[6] Major shortcomings of that procedure were the low, albeit acceptable, yield of the macrocyclization step, leading to a mixture of isomers, as well as the laborious preparation of the diester itself. As a result, this approach was no further considered, while different strategies were investigated to obtain 3,8-secotaxane diterpenoids.

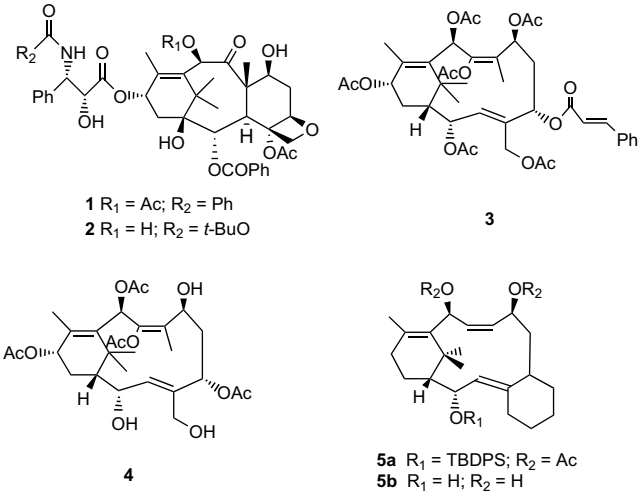
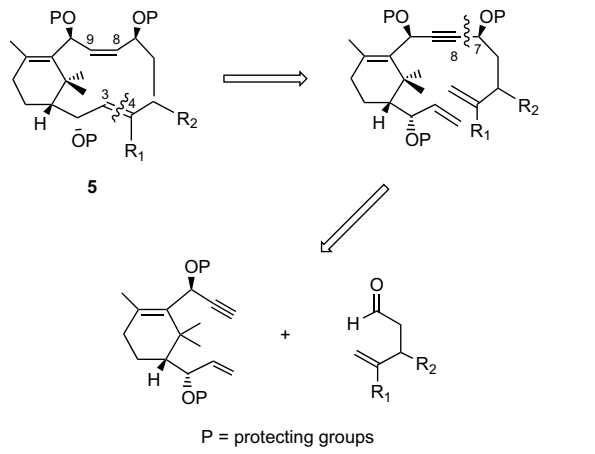


Figure 1.

Keywords: Taxuspine analogues; Synthesis; Macrocyclization; Ring closing metathesis.

* Corresponding author. Tel.: +39-0577234306; fax: +39-0577234333; e-mail: botta@unisi.it

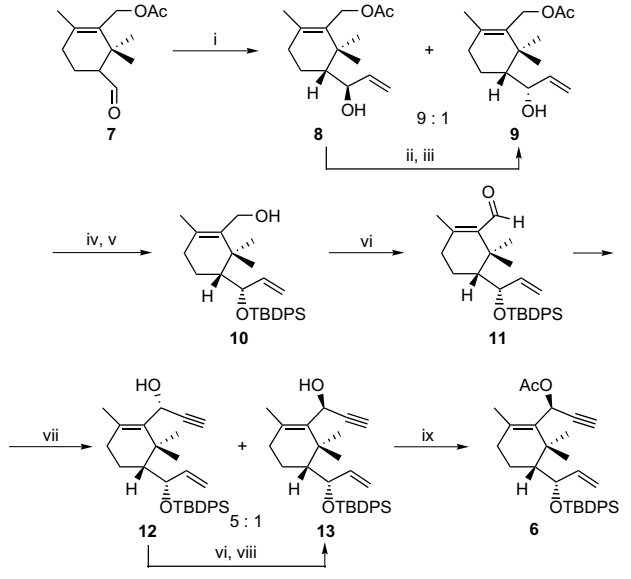
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.04.147



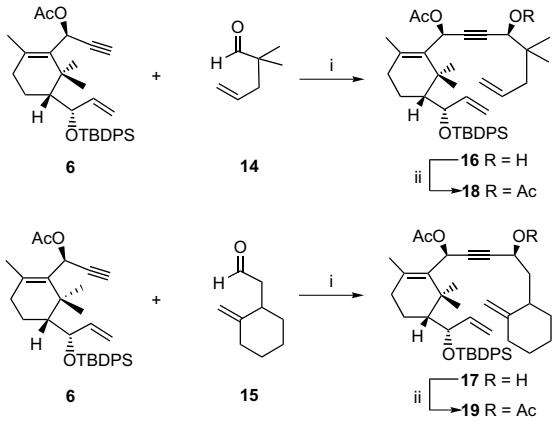
Scheme 1.

In this communication, we describe the synthesis of the Taxuspine X analogs **5** via an original, convergent approach, involving a ring closing metathesis (RCM) reaction[7] as the crucial step. The general features of our synthesis of **5** are outlined retrosynthetically in Scheme 1. Disconnection of the macrocycle between C3–C4 provides an ω,ω′-diolefine intermediate, which, in the synthetic direction, can be subjected to an RCM reaction, while the *cis*-$\Delta^{8,9}$ double bond is expected to result from selective reduction of the corresponding triple bond. Retrosynthetic cleavage of C7–C8 furnished an alkyne derivative and an aldehyde as potential precursors.

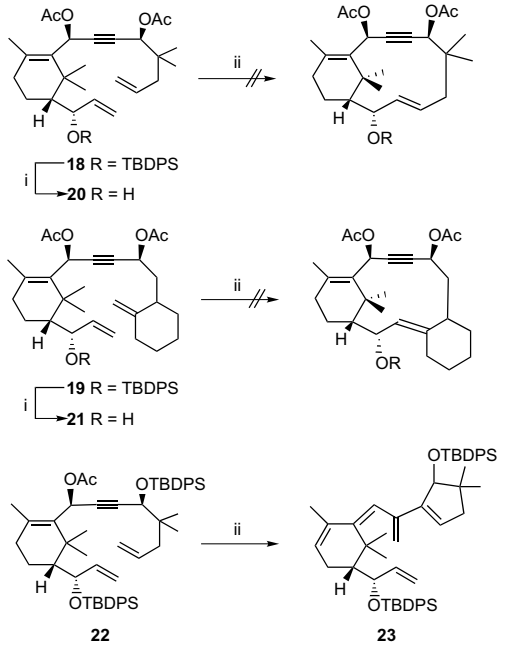
The alkyne precursor **6** was prepared according to Scheme 2. Treatment of the known aldehyde **7**[8] with a small excess of vinylmagnesium bromide, at low temperature, led to a 9:1 mixture of **8** and **9**,[9] respectively, the good level of diastereoselectivity resulting from the preferential attack of the nucleophile opposite to the *gem*-dimethyl group, with the carbonyl group also oriented away from these substituents, as reported in the literature for the addition of a nucleophile to **7**.[10] The most abundant *syn* isomer **8** was easily converted into **9** by oxidation with Dess–Martin periodinane, followed by reduction to alcohol of the ketone intermediate using L-Selectride.[11] Orthogonal protection of the allylic alcohol **9** as TBDP silyl ether,[12] followed by basic hydrolysis of the *O*-acetyl group, provided the primary alcohol **10**, which by oxidation with TPAP-MNO[13] was in turn converted into the aldehyde **11** in 95% yield. When the aldehyde **11** was reacted with ethynylmagnesium bromide, a mixture of two diastereoisomers **12** and **13** was obtained in a ratio of 5:1. This stereochemical result arose from the preferred approach of the Grignard reagent from the top of the molecule with the carbonyl group oriented downward in order to minimize the interaction with the adjacent methyl groups.[14] The resulting propargyl alcohols **12** and **13** were separated by chromatography and **12** was converted into the desired isomer **13** by oxidation to ketone with TPAP-MNO, followed by reduction with 9-BBN.[15] The propargyl alcohol **13** was finally acetylated to give the intermediate **6**.[16] The coupling reaction of **6** (Scheme 3) was performed on easily accessible γ,δ-unsaturated aldehydes, namely the commercially available 2,2-dimethyl-4-pentenaldehyde **14** and the easily obtainable 2-(2-methylenecyclohexyl)acetaldehyde **15**,[17] which are representative of a wide range of structural possibility for medicinal chemistry studies. Reaction of the organolithium derivative of **6** with aldehydes **14** and **15** afforded the intermediates **16** and **17** together with 30% of the diastereoisomers in which the C-7 hydroxy group was α-oriented. The isomers were separated by chromatography and the relative stereochemistry at C-7 was investigated by combination of the COSY, NOESY, and molecular mechanics data, which are in complete agreement with the published data for Taxuspine U and X,[18] while the C-5 stereochemistry of **17** has not been yet



Scheme 2. Reagents, conditions and yields: (i) vinylmagnesium bromide, THF, −78 °C to rt, 84%; (ii) Dess–Martin periodinane, CH_2Cl_2, 90%; (iii) L-Selectride, THF, −78 °C to rt, 84%; (iv) TBDPSCl, imidazole, DMAP, DMF rt, 85%; (v) K_2CO_3, CH_3OH, quantitative; (vi) TPAP, MNO, mol. siev., CH_2Cl_2, rt, 91%; (vii) ethynylmagnesium bromide, THF, −78 °C to rt, 85%; (viii) 9-BBN, THF, 0 °C, 90%; (ix) Ac_2O, Et_3N, DMAP, CH_2Cl, rt, quantitative.



Scheme 3. Reagents, conditions and yields: (i) LHMDS, THF, −78 °C to rt, 65–72%; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, quantitative.



Scheme 4. Reagents, conditions and yields: (i) TBAF, THF, 40 °C, 95%; (ii) Grubbs I or Grubbs II ruthenium catalyst, CH_2Cl_2, 40 °C, 66%.

determined. Compounds **16** and **17** in turn were converted into the macrocycle precursors **18** and **19** by acetylation of the newly formed alcohol group.

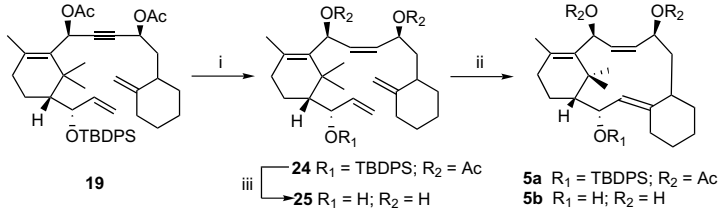
With these original macrocycle precursors in our hands, we went on to study the key reaction of our synthetic sequence. Different RCM assays were performed on the intermediate **18** and **19** (Scheme 4), but in no case intramolecular cyclization occurred and the unaltered starting material was consistently recovered, irrespective of the RCM conditions and the ruthenium catalyst (Grubbs I or Grubbs II catalyst) used. In order to reduce the sterical hindrance of the double bond and to help complexation to the catalyst, the silyl ether in the allylic position of **18** and **19** was cleaved to give the corresponding alcohols **20** and **21**, but also these substrates proved to be unreactive under the RCM conditions we adopted. On the other hand, when a more electron rich compound **22**, obtained by sylilation of **16**, was subjected to the same RCM conditions, a smooth reaction occurred, entailing intramolecular enyne metathesis followed by elimination of acetic acid and rearrangement of the double bonds, to provide compound **23**, characterized by a more stable conjugated system.[19,20] The difficulties we met in obtaining the RCM products were clearly not dependent on the sterical hindrance of the double bonds involved in this reaction. We reasoned that the alkyne function present in the precursors **16**–**22** could affect the catalyst, thus wrecking our plans of RCM. To the best of our knowledge, in fact, no other example of olefine metathesis has been carried out on substrates bearing an alkyne functionality. Accordingly, we decided to reduce the triple bond of **16**, **18**, and **19** to obtain the corresponding *cis*-alkenes. The results of the hydrogenation of **16** and **18** were largely dependent on the catalyst used, though in no case satisfactory. Thus, hydrogenation of these compounds in the presence of Lindlar catalyst only led to reduction of the less hindered double bond (right hand of the molecules),[21] whereas the use of Pd/$BaSO_4$/quinoline as the catalyst furnished the *cis*-$\Delta^{8,9}$ alkene derivatives of **16** and **18**, in which also both the ω,ω′-double bonds were completely hydrogenated.

Conversely, the partial hydrogenation of **19** to the corresponding *cis*-alkene with Lindlar catalyst and quinoline proved to be effective and the new macrocycle precursor **24** was obtained in 90% yield (Scheme 5). Finally, RCM reaction on **24** using Grubbs II catalyst gave in 20% yield the desired macrocycle **5a**,[22] a 3,8-secotaxane diterpenoid that represent the first analogue of Taxuspine X ever described. Similar results were obtained in the macrocyclization of **25**, the fully deprotected derivative of **24**, which could be converted into the tricyclic compound **5b** (25% yield).[23] COSY correlations of the final compounds confirmed the C-7 stereochemistry assigned.

In conclusion, we have developed a new and efficient methodology for the synthesis of simplified Taxuspines analogues. This methodology involves a macrocyclization via RCM that is effective in the presence of either free or protected hydroxy groups. The reported synthesis is the beginning of a wider project aimed at designing and synthesizing new microtubules-stabilizing antimitotic compounds and MDR-reversing agents.

Acknowledgements

We are grateful to the Research Training Network (HPRN-CT-2000-00018) 'Design and Synthesis of Novel Paclitaxel (Taxol®) Mimics Using a Common Pharmacophore Model for Microtubule-Stabilizing

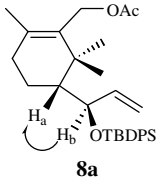


Scheme 5. Reagents, conditions and yields: (i) H_2, Lindlar catalyst, quinoline, petroleum ether, 90%; (ii) Grubbs II ruthenium catalyst, CH_2Cl_2, 20–25%; (iii) a: TBAF, THF, 40 °C, 75%; b: K_2CO_2, CH_3OH, quantitative.

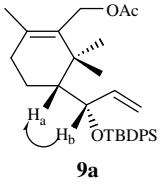
Agents (MSAAs)', FIRB (RBAU01LR5P) 'Development of a Common Pharmacophore Model for Microtubule-Stabilizing Anticancer Agents to be used to Design and Synthesise Novel Paclitaxel Mimics' and Indena S.p.A. for the financial support. We also thank Dr. L. Chiasserini for the NMR experiments (Bruker DRX 600 MHz Avance).

References and notes

1. Morihara, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980–12981, and references cited therein.
2. (a) Zamir, L. O.; Zhou, Z. H.; Caron, G.; Nedea, M. E.; Sauriol, F.; Mamer, O. *J. Chem. Soc., Chem. Commun.* **1995**, *5*, 529–530; (b) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3393–3396; (c) Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 3397–3400.
3. (a) Maccari, L.; Manetti, F.; Corelli, F.; Botta, M. *Il Farmaco* **2003**, *58*, 659–668; (b) 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.
4. PrGen, version 2.1.1: Biographics Laboratory, Basel, Switzerland.
5. Kobayashi, J.; Shigemori, H. *Med. Res. Rev.* **2002**, *22*, 305–328.
6. Corelli, F.; Dei, D.; Menichincheri, M.; Snyder, J. P.; Botta, M. *Tetrahedron Lett.* **1997**, *38*, 2759–2762.
7. For recent reviews see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (b) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077; (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (d) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565–588; (e) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211–240; (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, *2*, 371–388; (h) Blechert, S.; Schuster, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056.
8. Hitchcock, S. A.; Houldsworth, S. J.; Pattenden, G.; Pryde, D. C.; Thomson, N. M.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, *19*, 3181–3206.
9. Spectroscopic and analytical data for all the new compounds are in agreement with the assigned structures.
10. Tjepkema, M. W.; Wilson, P. D.; Audrain, H.; Fallis, A. G. *Can. J. Chem.* **1997**, *75*, 1215–1224.
11. Winkler, J. D.; Bhattacharya, S. K.; Batey, R. A. *Tetrahedron Lett.* **1996**, *37*, 8069–8072.
12. The analysis of the ^{1}H NMR spectrum of the diastereomeric silyl ethers **8a** and **9a** showed the H_b signal at δ 4.44 as a broad doublet, with a very small (about 1.5 Hz) H_aH_b ^3J for **8a**, while a larger (about 2.5 Hz) H_aH_b ^3J was observed for **9a**. This difference between the H_aH_b ^3J values for **8a** and **9a**, even if quite small, is nevertheless diagnostic (see Ref. 10) and in agreement with conformational studies performed on **8a** and **9a** in $CHCl_3$, in order to calculate the Boltzmann averaged value of the vicinal H_a–H_b coupling constants, thus confirming that the Grignard reaction favored the less hindered side of aldehyde **7**, as described in the literature for very similar reaction (see Ref. 10).
13. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, *7*, 639–666.
14. Tjepkema, M. W.; Wong, T.; Wilson, P. D.; Fallis, A. G. *Can. J. Chem.* **1997**, *75*, 1542–1551.
15. Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197–1201.
16. It is worth pointing out that the 'wrong' stereoisomers **8** and **12** might be of help for subsequent SAR studies, once elaborated into the corresponding 3,8-secotaxane diterpenoids.
17. 2-(2-Methylenecyclohexyl)acetaldehyde (**15**) was obtained by alkylation of cyclohexanone with ethyl bromoacetate, Wittig olefination of the ketone group and final reduction with DIBAL of the ester functionality.
18. (a) Hosoyama, H.; Inubishi, A.; Katsui, T.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 13145–13150; (b) Shigemori, H.; Wang, X.-X.; Yoshida, N.; Kobayashi, J. *Chem. Pharm. Bull.* **1997**, *45*, 1205–1208.
19. For a review on enyne metathesis see: Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133–154.
20. Attempts to rationalize these results using computer modeling and energy minimizations data, in order to verify the statistical possibility to find conformers with the ω,ω′-double bonds at an appropriate distance for giving a new double bond, were not conclusive, suggesting that **18** and **19** were the best precursors of the macrocycles **5** (Bernardini C. Master Thesis, University of Siena, 2002).
21. Burgstahler, A. W.; Widiger, G. N. *J. Org. Chem.* **1973**, *38*, 3652–3653.
22. Compound **5a** has been characterized: IR (film): *v* 3080, 1740, 1660, 979 cm^{-1}. Electrospray MS *m/z* 691 [M+Na]$^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69–7.61 (m, 5H), 7.40–7.28 (m, 5H), 6.32 (d J = 5 Hz, 1H), 5.74 (dd J = 5, 7 Hz, 1H), 5.55 (dd J = 6, 7 Hz, 1H), 5.4 (m, 1H), 5.1 (d J = 10 Hz, 1H), 4.32 (dd J = 2.5, 10 Hz, 1H), 2.35–2.18 (m, 4H), 2.06 (s, 3H), 2.02 (s, 3H), 1.97–1.87 (m, 3H), 1.85 (s, 3H), 1.70–1.65 (m, 5H), 1.30–1.20 (m, 4H), 1.1 (s, 3H), 1.02 (s, 9H), 0.97 (s, 3H).
23. Compound **5b** has been characterized: IR (film): *v* 3440, 3080, 1660, 979 cm^{-1}. Electrospray MS *m/z* 369 [M+Na]$^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.6 (dd J = 5, 7 Hz, 1H), 5.5 (d J = 6 Hz, 1H), 5.45 (dd J = 7, 7.5 Hz, 1H), 5.15 (d J = 10 Hz, 1H), 4.45 (br d J = 10 Hz, 1H), 4.38 (dd J = 6, 7.5 Hz, 1H), 2.35–2.18 (m, 5H), 1.97–1.87 (m, 3H), 1.85 (s, 3H), 1.70–1.65 (m, 6H), 1.30–1.20 (m, 5H), 1.1 (s, 3H), 0.97 (s, 3H).



8a



9a