Available online at www.sciencedirect.com
ScienceDirect
Journal of Organometallic Chemistry 691 (2006) 5438–5443
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Synthesis of model BC bicycles of taxol using C10–C11 ring-closing metathesis strategy

Stéphanie Schiltz [a], Cong Ma [a], Louis Ricard [b], Joëlle Prunet [a,*]

[a] *Laboratoire de Synthèse Organique, UMR CNRS 7652, Ecole Polytechnique, DCSO, F-91128 Palaiseau, France*
[b] *Laboratoire Hétéroéléments et Coordination, UMR CNRS 7653, Ecole Polytechnique, DCPH, F-91128 Palaiseau, France*

Received 5 July 2006; received in revised form 21 August 2006; accepted 21 August 2006
Available online 1 September 2006

Abstract

Model BC ring-systems of taxol **23b** and **28b**, which lack an oxygenated substituent at C7, have been efficiently synthesized. The key step is a ring-closing metathesis (RCM) to form the 8-membered B ring between C10 and C11. Comparison of the metathesis reaction in this route with the RCM used in a previous study with similar substrates is highlighted.

Keywords: Taxol; Metathesis; Cyclization; Ruthenium

Taxol® **1** and Taxotere® **2** are very effective therapeutic agents for the treatment of breast and ovarian cancer [1]. Six research groups have completed the total synthesis of taxol, and numerous synthetic works have been published since its isolation [2]. In the course of our studies towards the synthesis of this molecule, we planned a semi-convergent retrosynthesis of compound **3**, which is an intermediate in Holton's synthesis (Scheme 1) [2h,2i]. The A ring would be installed at a late stage by an intramolecular aldol reaction on a diketone at C13 and C11 (compound **4**) [3]. Bicycle **5** would be formed by a ring-closing metathesis (RCM) that would close the B ring between C10 and C11. The metathesis precursor **6** would be prepared by addition of the lithium derivative of vinyl bromide **8** to aldehyde **7**. We wish to report here the synthesis of models of bicycle **5**, which lack the alkoxy group at C7 and the ketal function at C13 [4].

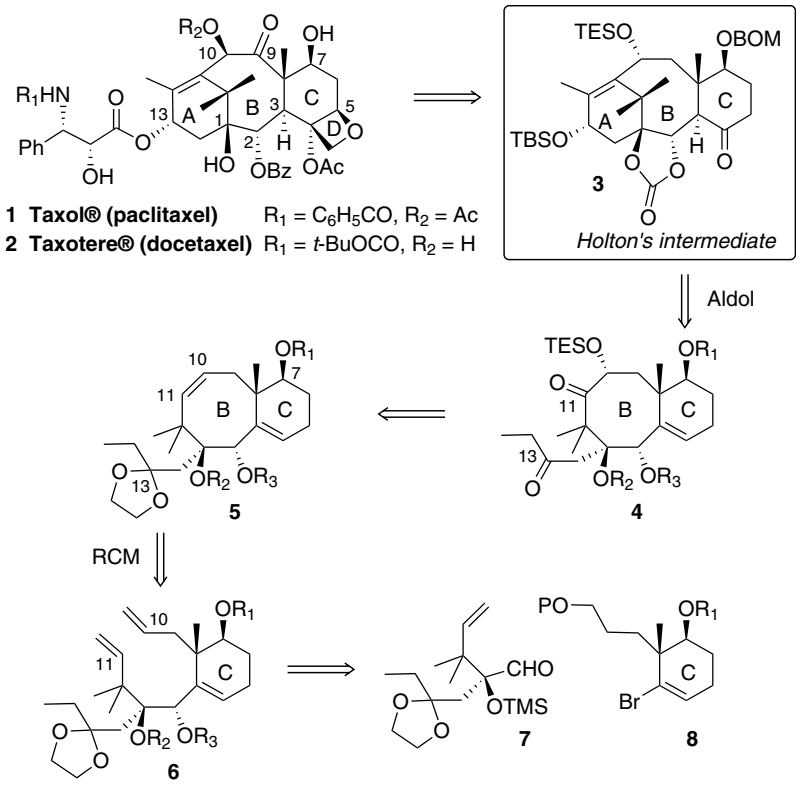
Model aldehyde **9** was prepared as a racemic mixture. Barbier reaction between isoprenyl bromide and valeraldehyde according to Luche's conditions [5], followed by oxidation with iodoxybenzoic acid [6], afforded ketone **10** in excellent overall yield. Homologation of this ketone to aldehyde **9** was effected by conversion to the corresponding cyanohydrin **11** ($TMSCN/ZnI_2$) and reduction by DIBAL-H [7] (Scheme 2).

Vinyl bromide **12** was synthesized as an enantiopure compound. The primary alcohol of known optically active diol **13** [8] was protected as its trityl ether [9]. Other protecting groups such as triisopropylsilyl (TIPS) or *p*-methoxybenzyl (PMB) ethers were also installed, but the yield of coupling between **9** and **12** revealed very dependent on this protecting group. We had originally planned to convert ketone **14** into vinyl bromide **12** by treatment of the corresponding hydrazone with NBS [10], but formation of the hydrazone is plagued by an important quantity of azine [11]. Ketone **14** was thus transformed into vinyl triflate **15** in excellent yield, and this compound afforded vinyl bromide **12** *via* the corresponding trimethylvinyl stannane derivative [12] (Scheme 3).

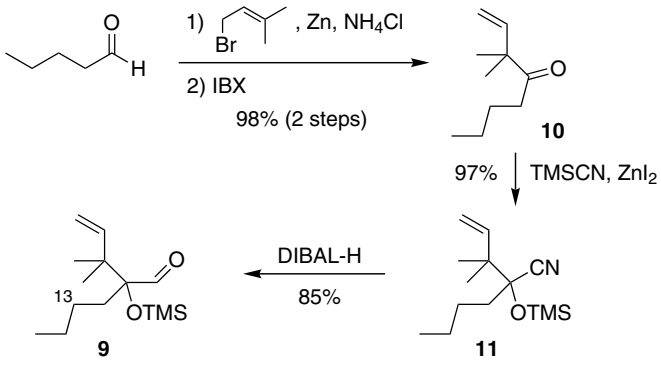
The coupling reaction of compounds **9** and **12** was then undertaken. Halogen-metal exchange was best performed by addition of a THF solution of bromide **12** into a solution of *t*-BuLi in THF. Subsequent addition of aldehyde

* Corresponding author. Tel.: +33 1 69 33 48 73; fax: +33 1 69 33 38 51.
E-mail address: joelle.prunet@polytechnique.fr (J. Prunet).

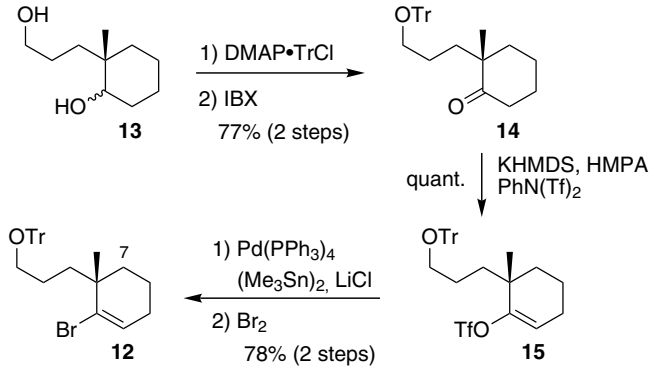
0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.08.078



Scheme 1.



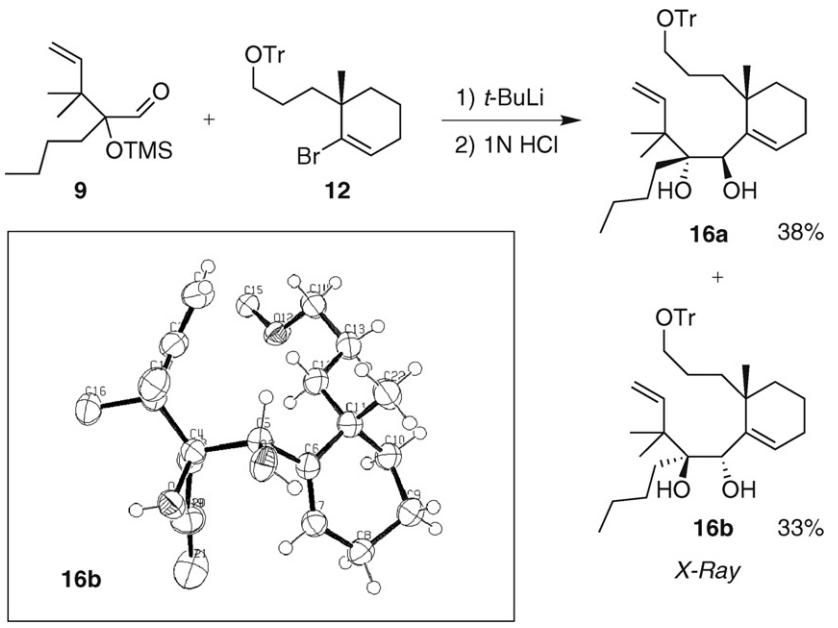
Scheme 2.



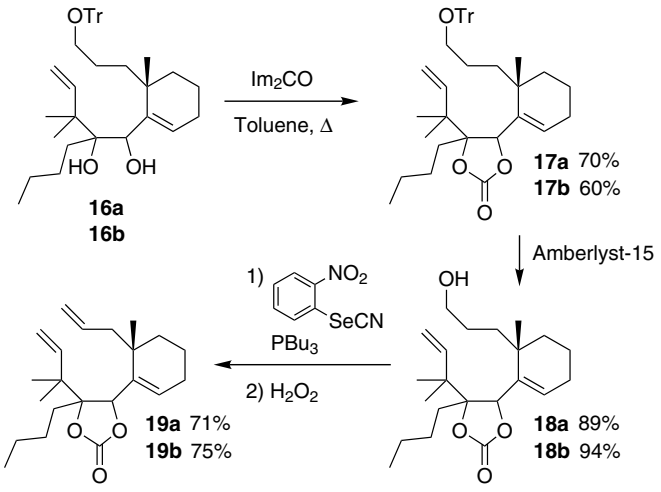
Scheme 3.

9 furnished the desired coupling product as a mixture of two diastereomers. Deprotection of the trimethylsilyl ether then gave diols **16a** and **16b**, which were easily separated by column chromatography (Scheme 4). The coupling reaction is very stereoselective, favoring the *trans* diols [13] (two isomers are obtained since the starting aldehyde is racemic). This diastereoselectivity had already been observed for similar coupling reactions performed in our laboratory during previous studies on taxol precursors [14]. The structures of both coupling products were secured by X-ray crystallographic analysis of diol **16b** for the desired diastereomer (Scheme 4), and of the derived triol **20a** for the other one [15].

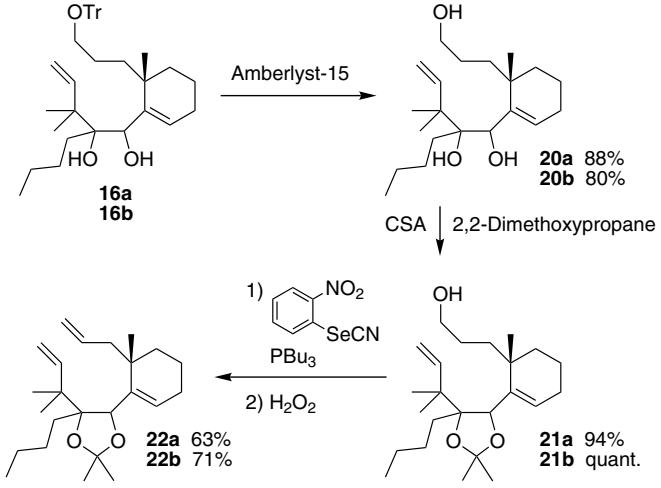
We decided to convert both isomers to substrates for the metathesis reaction, in order to compare the influence of the diol stereochemistry on the RCM. The primary trityl group had to be converted into a terminal olefin. Diols **16a** and **16b** were first protected as their carbonate derivatives **17a** and **17b**, respectively (Scheme 5). Treatment with sodium hydride and carbonyldiimidazole [4b] only gave the desired products in 10% yield, along with some decomposed material. Fortunately, **17a** and **17b** could be obtained by heating in toluene at reflux in the presence of carbonyldiimidazole only. The trityl group in **17a** and **17b** was first deprotected with formic acid, and the corresponding formate esters were dissolved in dioxane and hydrolyzed with 1 N aqueous sodium hydroxide, leading to alcohols **18a** and **18b** in 78% and 93% yield, respectively.



Scheme 4.



Scheme 5.

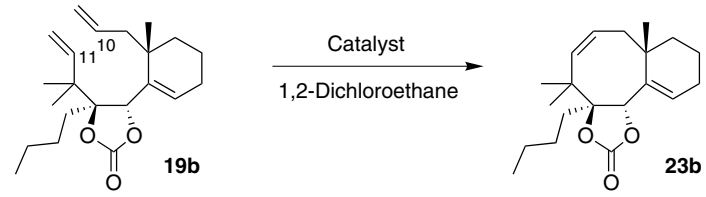


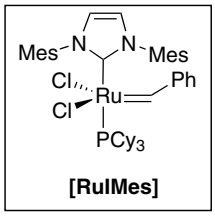
Scheme 6.

These compounds were obtained in a more direct fashion by treatment with Amberlyst-15 resin in methanol. The primary alcohols present in **18a** and **18b** were eliminated using Grieco's method [16], leading to the metathesis precursors **19a** and **19b**.

Metathesis precursors **22a** and **22b** where the diol moiety is protected as an acetonide were also synthesized (Scheme 6). Diols **16a** and **16b** were transformed into the corresponding triols **20a** and **20b** with Amberlyst-15 resin in methanol, and treatment of these compounds with 2,2-dimethoxypropane and CSA furnished acetonides **21a** and **21b** in good overall yields (83% and 80%, respectively). Grieco's method was then used as before, leading to the desired products **22a** and **22b**.

The ring-closing metathesis (RCM) experiments were first tested with carbonate **19a**, which possesses the wrong stereochemistry for taxol at C1 and C2. No cyclized product was observed with **Grubbs 1** [17] or **Grubbs 2** [18] catalyst in 1,2-dichloroethane at reflux, and prolonged reaction times (several days) with the latter complex only led to decomposition products. However, when diastereomer **19b** was submitted to 30 mol% of **Grubbs 1**, after several days at ambient temperature [19], the corresponding cyclooctene **23b** was produced in 65% yield as the *Z* isomer exclusively (Scheme 7). Use of second-generation catalysts **Grubbs 2** or **[RuIMes]** [20] furnished the same product in comparable yields (69% and 72%, respectively), but the reaction was much faster (1 h only).

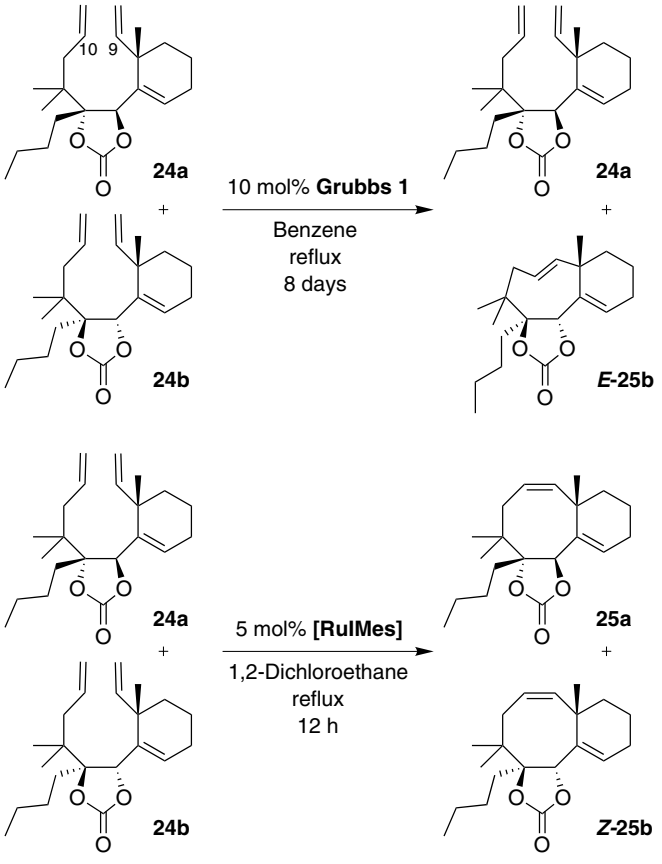




Catalyst	Temperature	Time	Yield
Grubbs 1 (30 mol%)	20°C	5 days	65%
Grubbs 2 (10 mol%)	80°C	1 h	69%
[RuIMes] (5 mol%)	80°C	1 h	72%

Scheme 7.

These results are in sharp contrast with those obtained during our previous route to BC ring-systems of taxol, where the RCM took place between the C9 and the C10 carbons instead of C10–C11 on otherwise similar substrates [4]. In those cases, the diastereomer presenting the wrong stereochemistry at the diol stereocenters (**24a**) did not cyclize with **Grubbs 1**, but produced the expected cyclooctene **25a** with **[RuIMes]** (Scheme 8) [21]. The other diastereomer (**24b**) led to the kinetic *trans* cyclooctene ***E*-25b** with **Grubbs 1**, and to the *cis* 8-membered ring ***Z*-25b** with **[RuIMes]**. It seems that metathesis is much more difficult for the wrong diastereomer when the ring-closing reaction occurs at C10–C11 (this paper) rather than at C9–C10 (previous study), and much easier for the desired diastereomer. Of course, one cannot directly compare the two reactions, because the first carbene is formed on opposite sides of the molecules in each case. In the first route, it is formed on C10, which is attached to the left-hand side of the molecule, and the reaction proceeds to close onto C9. In this work, the first carbene is formed on C10, but this carbon is attached to the right-hand side of the precursor, and ring-closure occurs at C11.

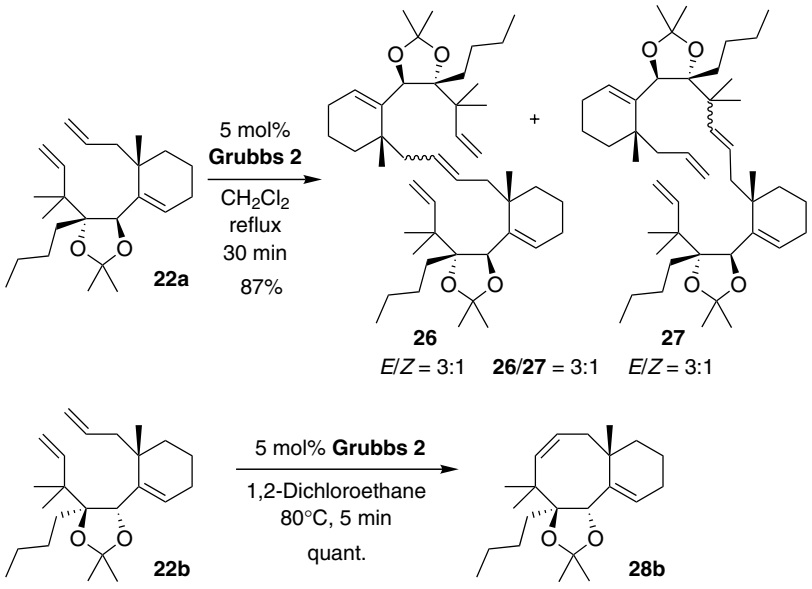


Scheme 8.

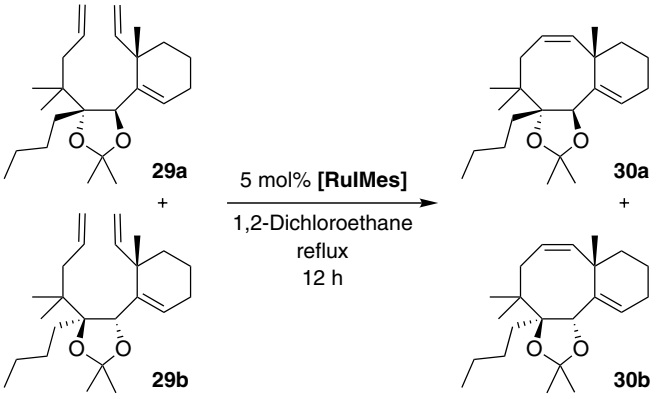
Finally, the acetonide derivatives were subjected to **Grubbs 2** catalyst. After 30 min in CH_2Cl_2 at reflux, diastereomer **22a** only led to dimeric products **26** and **27** in a 3:1 ratio, favoring the symmetrical product (Scheme 9). Each dimer was produced as a 3:1 mixture of diasteromers. Cyclization of the other diastereomer **22b** was exceptionally fast, and bicycle **28b** was obtained in quantitative yield after only 5 min in 1,2-dichloroethane at reflux.

Here also, the same comparison can be made with the RCM reactions of acetonides **29a** and **29b** from the previous study, which both cyclized with **[RuIMes]** after 12 h in 1,2-dichloroethane at reflux (Scheme 10). In the second route, cyclization with the wrong diastereomer is not possible, and much faster for the isomer which leads to model BC ring-systems of taxol.

In conclusion, we have synthesized highly functionalized cyclooctenes that are model precursors of taxol, using a ring-closing metathesis at C10–C11 to form the B ring. Direct comparison of this route with a previous study involving RCM at C9–C10 shows that the metathesis step works much more efficiently for the diastereomers useful for the synthesis using the C10–C11 strategy. We are currently preparing metathesis precursors with all the required functionalities for taxol.



Scheme 9.



Scheme 10.

Acknowledgements

Financial support was provided by the CNRS and the Ecole Polytechnique. S.S. acknowledges the Délégation Générale pour l'Armement (DGA) for a fellowship. We thank Dr. Ange Pancrazi for helpful discussion.

References

[1] N.H. Oberlies, D.J. Kroll, J. Nat. Prod. 67 (2004) 129.
[2] For reviews on the chemistry of taxol, see: (a) K.C. Nicolaou, W.-M. Dai, R.K. Guy, Angew. Chem., Int. Ed. Engl. 33 (1994) 15;
(b) D.G.I. Kingston, Chem. Commun. (2001) 867;
For the total syntheses, see: (c) K.C. Nicolaou, Z. Yang, J.J. Liu, H. Ueno, P.G. Nantermet, R.K. Guy, C.F. Claiborne, J. Renaud, E.A. Couladouros, K. Paulvannan, E.J. Sorensen, Nature 367 (1994) 630;
(d) K.C. Nicolaou, P.G. Nantermet, H. Ueno, R.K. Guy, E.A. Couladouros, E.J. Sorensen, J. Am. Chem. Soc. 117 (1995) 624;
(e) K.C. Nicolaou, J.J. Liu, Z. Yang, H. Ueno, E.J. Sorensen, C.F. Claiborne, R.K. Guy, C.K. Hwang, M. Nakada, P.G. Nantermet, J. Am. Chem. Soc. 117 (1995) 634;
(f) K.C. Nicolaou, Z. Yang, J.J. Liu, P.G. Nantermet, C.F. Claiborne, J. Renaud, R.K. Guy, K. Shibayama, J. Am. Chem. Soc. 117 (1995) 645;
(g) K.C. Nicolaou, H. Ueno, J.J. Liu, P.G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, R. Chadha, J. Am. Chem. Soc. 117 (1995) 653;
(h) R.A. Holton, C. Somoza, H.B. Kim, F. Liang, R.J. Biediger, P.D. Boatman, M. Shindo, C.C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K.K. Murthi, L.N. Gentile, J.H. Liu, J. Am. Chem. Soc. 116 (1994) 1597;
(i) R.A. Holton, H.B. Kim, C. Somoza, F. Liang, R.J. Biediger, P.D. Boatman, M. Shindo, C.C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K.K. Murthi, L.N. Gentile, J.H. Liu, J. Am. Chem. Soc. 116 (1994) 1599;
(j) J.J. Masters, J.T. Link, L.B. Snyder, W.B. Young, S. Danishefsky, Angew. Chem., Int. Ed. Engl. 34 (1995) 1723;
(k) P.A. Wender, N.F. Badham, S.P. Conway, P.E. Floreancig, T.E. Glass, C. Gränicher, J.B. Houze, J. Jänichen, D. Lee, D.G. Marquess, P.L. McGrane, W. Meng, T.P. Mucciaro, M. Mühlebach, M.G. Natchus, H. Paulsen, D.B. Rawlins, J. Satkofsky, A.J. Shuker, J.C. Sutton, R.E. Taylor, K. Tomooka, J. Am. Chem. Soc. 119 (1997) 2755;
(l) P.A. Wender, N.F. Badham, S.P. Conway, P.E. Floreancig, T.E. Glass, J.B. Houze, N.E. Krauss, D. Lee, D.G. Marquess, P.L. McGrane, W. Meng, M.G. Natchus, A.J. Shuker, J.C. Sutton, R.E. Taylor, J. Am. Chem. Soc. 119 (1997) 2757;
(m) T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, H. Nishimura, Y.-I. Tani, M. Hasegawa, K. Yamada, K. Saito, Chem. Eur. J. 5 (1999) 121;
(n) K. Morihara, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, I. Kuwajima, J. Am. Chem. Soc. 120 (1998) 12980.
[3] C.S. Swindell, B.P. Patel, J. Org. Chem. 55 (1990) 3.
[4] For previous work from this laboratory on syntheses of model BC ring-systems of taxol involving RCM between C9 and C10, see: (a) D. Bourgeois, A. Pancrazi, L. Ricard, J. Prunet, Angew. Chem., Int. Ed. Engl. 39 (2000) 725;
(b) D. Bourgeois, J. Mahuteau, A. Pancrazi, S.P. Nolan, J. Prunet, Synthesis (2000) 869.
[5] C. Pétrier, J.-L. Luche, J. Org. Chem. 50 (1985) 12.
[6] M. Frigerio, M. Santagostino, S. Sputore, J. Org. Chem. 64 (1999) 4537.
[7] For a similar homologation, see Ref [4b] and: B. Muller, F. Delaloge, M. den Hartog, J.-P. Férézou, A. Pancrazi, J. Prunet, J.-Y.

Lallemand, A. Neuman, T. Prangé, Tetrahedron Lett. 37 (1996) 3313.
[8] J. Boukouvalas, Y.-X. Cheng, J. Robichaud, J. Org. Chem. 63 (1998) 228.
[9] O. Hernandez, S.K. Chaudhary, R.H. Cox, J. Porter, Tetrahedron Lett. 22 (1981) 1491.
[10] A. Pross, S. Sternbell, Aust. J. Chem. 23 (1970) 989.
[11] A. Pross, S. Sternbell, Aust. J. Chem. 24 (1971) 1437.
[12] L.A. Paquette, S. Liang, H.-L. Wang, J. Org. Chem. 61 (1996) 3268.
[13] Diols **16a** and **16b** would be *trans* if the B ring were closed.
[14] D. Bourgeois, G. Maiti, A. Pancrazi, J. Prunet, Synlett (2000) 323.
[15] Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 613208 for compound **16b** and No. 613209 for compound **20a**.
[16] (a) P.A. Grieco, S. Gilman, M. Nishizawa, J. Org. Chem. 41 (1976) 1485;
(b) P. de Armas, F. Garcia-Tellado, J.J. Marrero-Tellado, Eur. J. Org. Chem. (2001) 4423.
[17] (a) P. Schwab, M.B. France, J.W. Ziller, R.H. Grubbs, Angew. Chem., Int. Ed. Engl. 34 (1995) 2039;
(b) P. Schwab, R.H. Grubbs, J.W. Ziller, J. Am. Chem. Soc. 118 (1996) 100.
[18] M. Scholl, S. Ding, C.W. Lee, R.H. Grubbs, Org. Lett. 1 (1999) 953.
[19] Reaction was started with 10 mol% catalyst, and 5 mol% additional catalyst was added every day.
[20] (a) J. Huang, E.D. Stevens, S.P. Nolan, J.L. Petersen, J. Am. Chem. Soc. 121 (1999) 2674;
(b) M. Scholl, T.M. Trnka, J.P. Morgan, R.H. Grubbs, Tetrahedron Lett. 40 (1999) 2247.
[21] The RCM reactions depicted on Scheme 8 were performed on mixtures of **24a** and **24b**, as these diastereomers are inseparable by chromatography on silica gel.