Organic LETTERS

Letter

pubs.acs.org/OrgLett

Highly Efficient Synthesis of the Tricyclic Core of Taxol by Cascade Metathesis

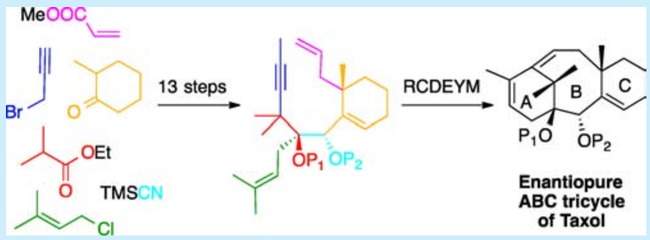
Aurélien Letort,[†] Rémi Aouzal,[‡,§] Cong Ma,[‡,∥] De-Liang Long,[†] and Joëlle Prunet*[,†]

[†]WestCHEM, School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, U.K.

[‡]Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole Polytechnique, DCSO, 91128 Palaiseau, France

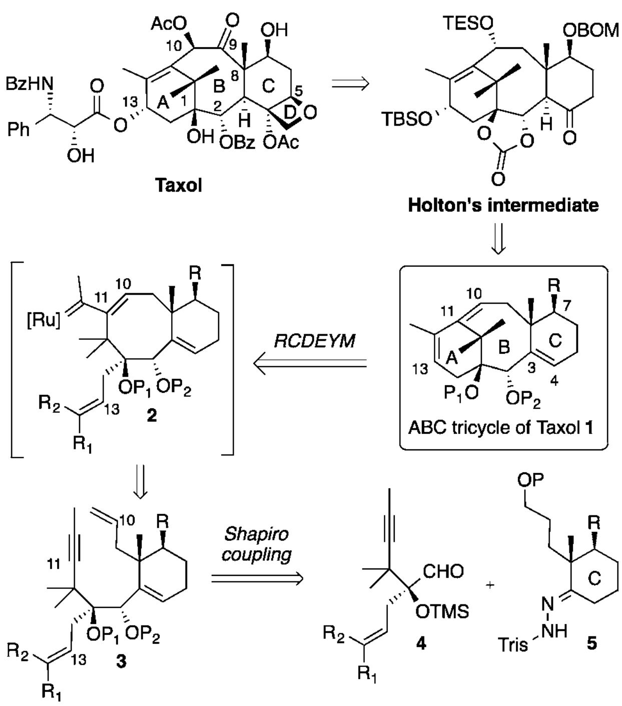
Supporting Information

ABSTRACT: An efficient enantioselective synthesis of the ABC tricyclic core of the anticancer drug Taxol is reported. The key step of this synthesis is a cascade metathesis reaction, which leads in one operation to the required tricycle if appropriate fine-tuning of the dienyne precursor is performed.



Taxol (Scheme 1) and its derivatives are the largest selling anticancer drugs of all time,[1] and they are employed to treat a wide range of malignancies.[2] There have been six total syntheses of Taxol by the groups of Holton,[3] Nicolaou,[4] Danishefsky,[5] Wender,[6] Mukaiyama,[7] and Kuwajima,[8] as well as one formal synthesis by Takahashi et al.[9] Other elegant approaches leading to the ABC tricyclic core of taxane derivatives include work by the groups of Swindell,[10] Pattenden,[11] Granja,[12] Winkler,[13] and Baran.[14] In our approach toward Taxol,[15] we aimed for a compound described by Holton et al.[3b] (Scheme 1). This intermediate could be synthesized from compound **1** (R = OBOM), using Danishefsky's route to convert the C3−C4 alkene into the ketone[5] and Granja's method to install the 11-ene-10,13 diol from the C10−C13 diene.[16] Herein, we report a synthetic strategy to the ABC tricyclic core of Taxol **1**, featuring a challenging cascade ene-yne-ene ring-closing metathesis (RCDEYM) reaction[17] that allows a highly efficient access to this compound. Although such a cascade metathesis has already been employed by Granja's[12] and our group[18] for the synthesis of model ABC tricycle of taxoids, in each case the relative stereochemistry of these analogues at C1, C2, and C8 was different from the one found in Taxol. Moreover, the *gem* dimethyl group bridging the A and B rings, whose steric hindrance presents a major difficulty in the synthesis of Taxol, was either not present[12] or not positioned at the proper place.[18]

Scheme 1. Retrosynthesis of Taxol

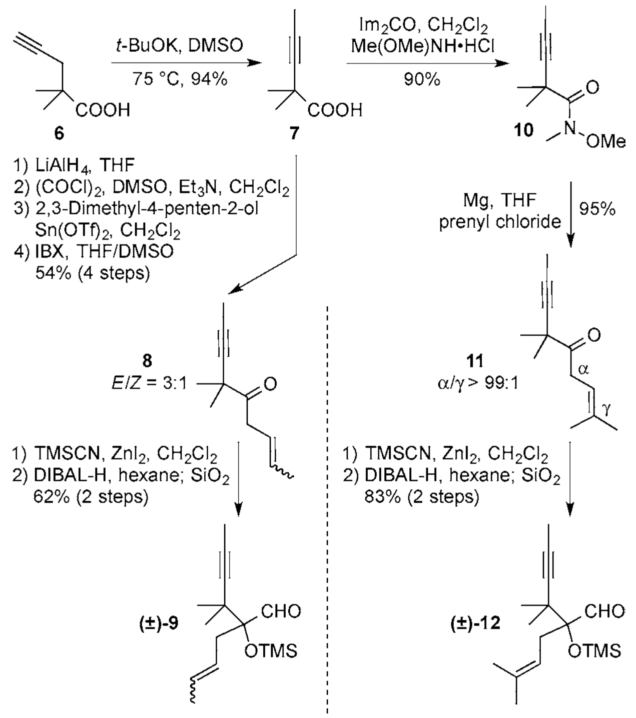


We elected to validate our approach on the 7-deoxy ABC ring system **1** (R = H) (Scheme 1). Enyne metathesis of compound **3** between the alkene at C10 and the alkyne at C11 would produce the intermediate carbene **2**, which would lead to compound **1** after subsequent diene RCM. In order to direct the metathesis cascade so it will start with the olefin at C10, we chose to have a di- or trisubstituted olefin at C13 (R_1 = Me, R_2 = H, Me), which would react more slowly with the metathesis catalysts. Dienyne **3** would be constructed by a Shapiro coupling between aldehyde **4** and hydrazone **5**.

The synthesis of the required aldehydes started from the known acid **6**[19] (Scheme 2), which is easily prepared from ethyl isobutyrate in two steps (81% overall yield). Isomerization of the terminal alkyne into the more stable internal alkyne was performed by heating **6** at 75 °C in DMSO in the presence of potassium *tert*-butoxide[20] in 93% yield, and the acid **7** was then

Received: May 7, 2014
Published: June 5, 2014

Scheme 2. Synthesis of Aldehydes (±)-9 and (±)-12 for Shapiro Coupling

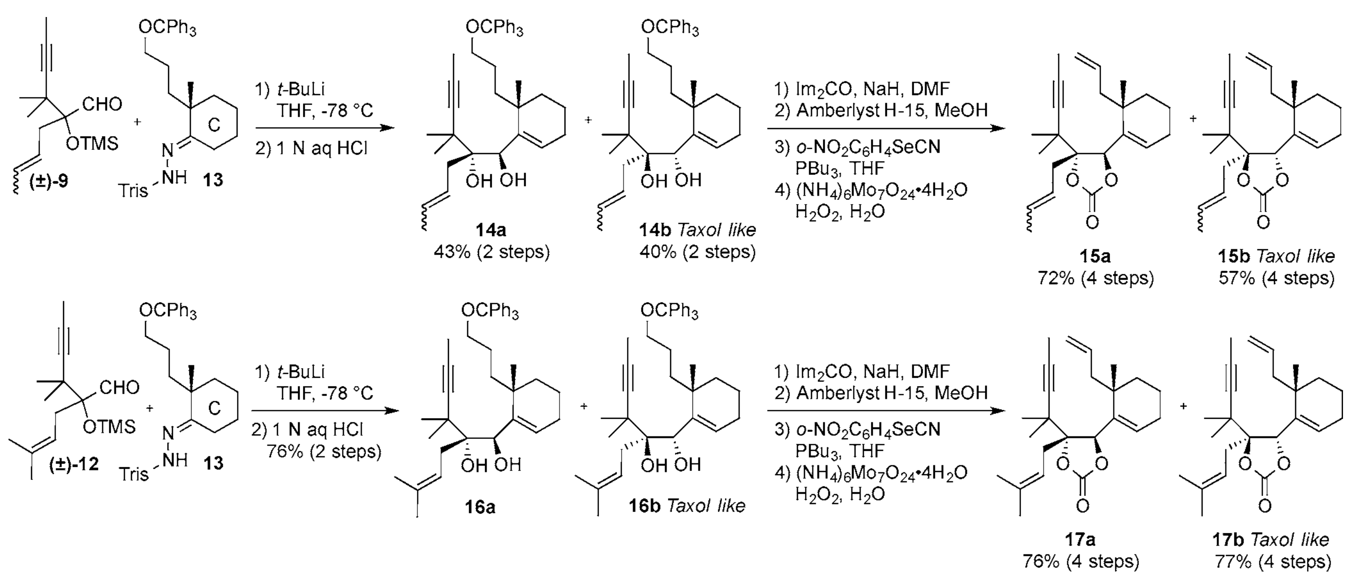


converted into ketone **8** in 4 steps as a 3:1 mixture of *E* and *Z* isomers.[21] This ketone was then submitted to trimethylsilyl cyanide in the presence of a catalytic amount of zinc diiodide. The resulting cyanohydrin was reduced with DIBAL-H to the intermediate imine, which was hydrolyzed to the racemic aldehyde (±)-**9** by exposure to silica gel. Acid **7** was also converted into the corresponding Weinreb amide **10**, and addition of prenylmagnesium chloride to this amide furnished ketone **11** in 95% yield as the *α* prenylation isomer only. Cyanosilylation of ketone **11** followed by reduction of the resulting cyanohydrin with DIBAL-H gave aldehyde (±)-**12** in excellent overall yield. Enantiopure aldehydes **9** and **12** could be prepared using an enantioselective cyanation reaction,[18] but we chose to pursue the synthesis of the metathesis precursors with the racemic aldehyde to study the influence of the stereochemistry of the precursors on the RCDEYM reaction outcome.

Hydrazone **13**[15h] (Scheme 3) was reacted with aldehyde (±)-**9** using the conditions we developed previously.[15h] As had been observed for model aldehydes,[15d] this reaction was highly diastereoselective, giving compounds **14a** and **14b** after hydrolysis of the trimethylsilyl ether in excellent combined yield. These diols **14a** and **14b** were then submitted separately to the protection of the C1−C2 diol as the cyclic carbonate, triphenylmethyl ether hydrolysis, and dehydration of the resulting primary alcohol using the Grieco protocol[22] to furnish the metathesis precursors **15a** and **15b** in 72% and 57% overall yield for the four steps, respectively. When the aldehyde (±)-**12** was engaged in the Shapiro coupling, the *trans* diols **16a** and **16b** were obtained in 76% combined yield (Scheme 3). These diols were separately converted into the corresponding carbonates **17a** and **17b** in 76% and 77% overall yield, respectively, using the same protocols as that for the synthesis of **15a** and **15b**.

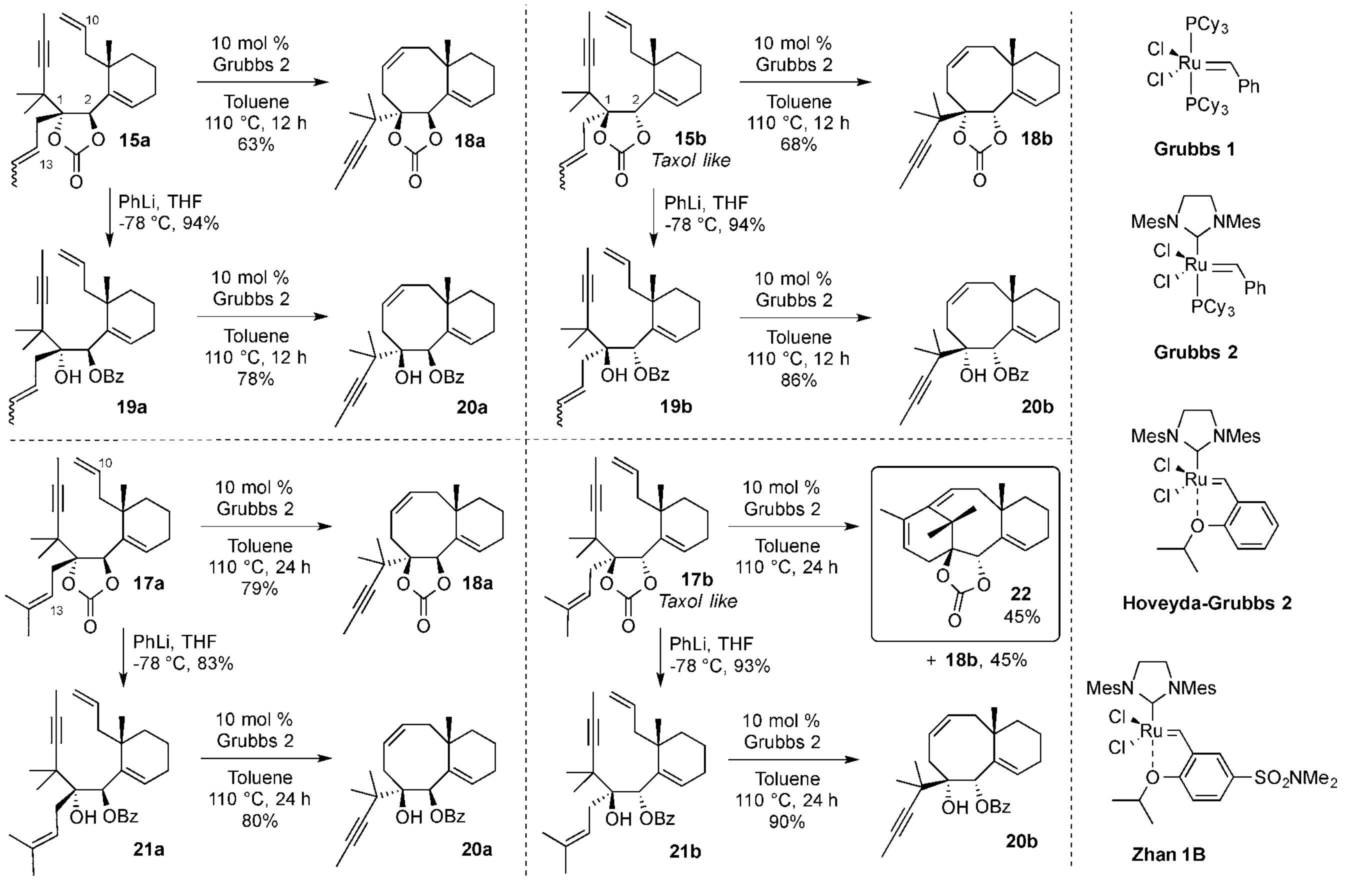
The key metathesis step was then studied. Carbonates **15a** and **15b** both failed to produce tricyclic products, but led to the bicycles **18a** and **18b** resulting from a diene metathesis reaction between the olefins at C10 and C13 (Scheme 4). These carbonates were converted to the corresponding benzoates **19a** and **19b** by treatment with phenyllithium, as we have shown that the nature of the diol protecting group plays a crucial role in the outcome of metathesis reactions leading to BC ring systems of taxol.[15h] These benzoates **19a,b** also underwent diene metathesis, and the bicyclic benzoates **20a** and **20b** were obtained in very good yields. *E* and *Z* isomers of **15a,b** and **19a,b** exhibited the same behavior. We concluded that the steric hindrance around the alkyne was disfavoring the initial enyne metathesis for all these substrates. Since the *gem*-dimethyl group is an inherent part of the Taxol skeleton, it was impossible to decrease this unfavorable steric hindrance. However, we reasoned that the increased steric hindrance of the alkene at C13 of compounds **17a,b** and **21a,b** (Scheme 4)

Scheme 3. Synthesis of Metathesis Precursors 15a,b and 17a,b



dx.doi.org/10.1021/ol501304j | Org. Lett. 2014, 16, 3300−3303

Scheme 4. Attempts at RCDEYM and Synthesis of the ABC Tricycle of Taxol

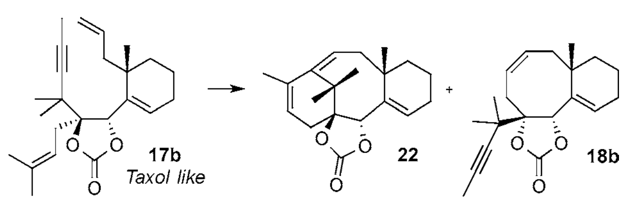


should disfavor the undesired initial diene metathesis. This hypothesis proved false for both the carbonate and the benzoate compounds **17a** and **21a** possessing the undesired configuration at the C1 and C2 positions as well as for the Taxol-like benzoate **21b**, which led to the carbonate **18a** and the benzoates **20a** and **20b**, respectively (Scheme 4). Remarkably, reaction of the Taxol-like carbonate **17b** with Grubbs' second-generation catalyst[23] in toluene at reflux furnished the desired tricyclic core of Taxol **22** in 45% yield,[24] along with 45% of the product of diene metathesis **18b**.[25]

We then varied the reaction conditions in order to optimize the yield of compound **22** (Table 1). Lowering the reaction concentration did not change the ratio of **22** and **18b** (entry 1 vs 2). Different catalysts were then evaluated. Unsurprisingly, the Grubbs 1 catalyst[26] was not active enough to perform any metathesis reaction (entry 3). The yield of **22** increased to 59% with the Hoveyda-Grubbs 2 complex[27] (entry 4), but the best yield (70%) was obtained with a variant of this catalyst bearing an electron-withdrawing group on the benzylidene ligand, the Zhan-1B catalyst[28] (entry 5), along with 20% of bicycle **18b**. Changing the nature of the solvent and the reaction temperature while using the Zhan-1B catalyst did not bring any improvement (entries 6–9). The reaction did not proceed in refluxing dichloromethane (40 °C), and only degradation was observed in refluxing xylene (140 °C). Interestingly, the reaction proceeded faster in refluxing 1,2-dichloroethane (80 °C) than in toluene at the same temperature (entry 7 vs 9).

In summary, we have constructed the ABC tricyclic core of Taxol in 14 steps and 11% overall yield from ethyl isobutyrate.

Table 1. Optimization of the RCDEYM



entry	catalyst	solvent[a]	[C] 10^{-3} M	yield (%) **22**:**18b**
1	Grubbs 2	toluene	15	45:45
2	Grubbs 2	toluene	3.5	40:40
3	Grubbs 1	toluene	5	0:0
4	HG 2	toluene	4	59:38
5	**Zhan-1B**	**toluene**	**3.2**	**70:20**
6	Zhan-1B	CH_2Cl_2	3.5	0:0
7	Zhan-1B	$Cl(CH_2)_2Cl$	3.5	65:34
8	Zhan-1B	xylene	3	degradation
9	Zhan-1B	toluene, 80 °C	3	40:10[b]

[a]Reaction run at solvent reflux unless otherwise stated. [b]Total yield: 50% (83% brsm).

The key step of this synthesis is an RCDEYM that leads in one operation to the required tricycle, and we have shown that we can direct the course of this metathesis reaction by adding an extra methyl substituent to the olefin at C13, which does not appear in the structure of the metathesis products. Both the nature of the protecting group and the stereochemistry of the diol at C1–C2 have a profound influence on the outcome of the metathesis reaction, and only the diastereomer with the required stereochemistry for Taxol for the C1–C2 diol,

dx.doi.org/10.1021/ol501304j | Org. Lett. 2014, 16, 3300–3303

protected as a cyclic carbonate, undergoes the desired RCDEYM. Calculations are in progress to rationalize these results, and work is currently underway to achieve the formal synthesis of Taxol.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, compound characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: joelle.prunet@glasgow.ac.uk.

Present Addresses

[§]PCAS, 23 rue Bossuet, ZI de la Vigne aux Loups 91160 Longjumeau, France.

[‖]Molecular Microbiology Biological Sciences School of Environmental and Life Sciences University of Newcastle Callaghan, NSW 2308 Australia.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the CNRS, the Ecole Polytechnique, and the University of Glasgow. We thank Dr. Brian Millward, Honorary Research Fellow, School of Chemistry, University of Glasgow, for a generous donation.

■ REFERENCES

(1) Yvon, D. Paclitaxel ranks first among world's anti-cancer drugs. *Marketing Articles [Online]*, Februay 28, 2012. http://www.articlesfactory.com/articles/marketing/paclitaxel-ranks-first-among-worlds-anti-cancer-drugs.html (accessed May 29, 2014).

(2) Yared, J. A.; Thaczuk, K. H. R. *Drug Des. Dev. Ther.* **2012**, 371.

(3) (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

(4) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630.

(5) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723.

(6) (a) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755. (b) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757.

(7) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad.* **1993**, *73B*, 95−100.

(8) Morihara, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980.

(9) Doi, T.; Fuse, S.; Miyamoto, S.; Nakai, K.; Sasuga, D.; Takahashi, T. *Chem.—Asian J.* **2006**, *1*, 370.

(10) Swindell, C. S.; Patel, B. P. *J. Org. Chem.* **1990**, *55*, 3.

(11) Goldring, P. D.; Pattenden, G.; Rimmington, S. L. *Tetrahedron* **2009**, *65*, 6670.

(12) (a) Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Org. Lett.* **2008**, *10*, 3789. (b) Aldegunde, M. J.; Garcia- Fandino, R.; Castedo, L.; Granja, J. R. *Chem.—Eur. J.* **2007**, *13*, 5135.

(13) Winkler, J. D.; Kim, H. S.; Kim, S. A. *Tetrahedron Lett.* **1995**, *36*, 687.

(14) (a) Mendoza, A.; Ishibara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21. (b) Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4909.

(15) (a) Muller, B.; Delaloge, F.; den Hartog, M.; Férézou, J.-P.; Pancrazi, A.; Prunet, J.; Lallemand, J.-Y.; Neuman, A.; Prangé, T. *Tetrahedron Lett.* **1996**, *37*, 3313. (b) Muller, B.; Férézou, J.-P.; Lallemand, J.-Y.; Pancrazi, A.; Prunet, J.; Prangé, T. *Tetrahedron Lett.* **1998**, *39*, 279. (c) Bourgeois, D.; Lallemand, J.-Y.; Pancrazi, A.; Prunet, J. *Synlett* **1999**, 1555. (d) Bourgeois, D.; Maiti, G.; Pancrazi, A.; Prunet, J. *Synlett* **2000**, 323. (e) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem.* **2000**, *112*, 741; *Angew. Chem., Int. Ed.* **2000**, *39*, 725−728. (f) Bourgeois, D.; Mahuteau, J.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *Synthesis* **2000**, 869. (g) Schiltz, S.; Ma, C.; Ricard, L.; Prunet, J. *J. Organomet. Chem.* **2006**, *691*, 5438. (h) Ma, C.; Schiltz, S.; Le Goff, X. F.; Prunet, J. *Chem.—Eur. J.* **2008**, *14*, 7314.

(16) Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Chem.—Eur. J.* **2009**, *15*, 4785.

(17) Kim, S.-H.; Bowden, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1994**, *116*, 10801.

(18) Ma, C. PhD Thesis, Ecole Polytechnique (Palaiseau, France), 2008.

(19) Yamazaki, Y.; Kido, Y.; Hidaka, K.; Yasui, H.; Kiso, Y.; Yakushiji, F.; Hayashi, Y. *Bioorg. Med. Chem.* **2011**, *19*, 595.

(20) Bourgeois, D.; Prunet, J.; Pancrazi, A.; Prangé, T.; Lallemand, J.-Y. *Eur. J. Org. Chem.* **2000**, 4029.

(21) See Supporting Information for details. Ketone **8** was also prepared by addition of crotylmagnesium chloride to amide **10**, but could not be obtained pure due to the quality of the crotyl chloride.

(22) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(23) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(24) X-ray diffraction analysis of a derivative of **22** established the tricyclic structure of the product and confirmed that it possesses the required relative configuration at C1, C2, and C8 for Taxol (see Supporting Information for details).

(25) Attempts to convert bicycle **18b** to the desired tricycle **22** by resubmitting it to the reaction conditions, with or without 2-methyl-2-butene were unsuccessful, and only recovered **18b** was obtained: Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939. These results seem to indicate that the formation of compound **18b** is not reversible under the reaction conditions.

(26) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039.

(27) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(28) Zhang, Z.-Y. J. U.S. Patent UP2007/0043180 A1.