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Toward an Efficient Synthesis of Taxane Analogs by Dienyne Ring-Closing Metathesis

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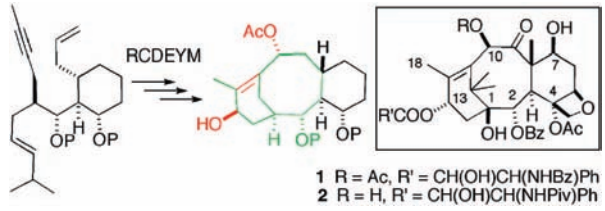
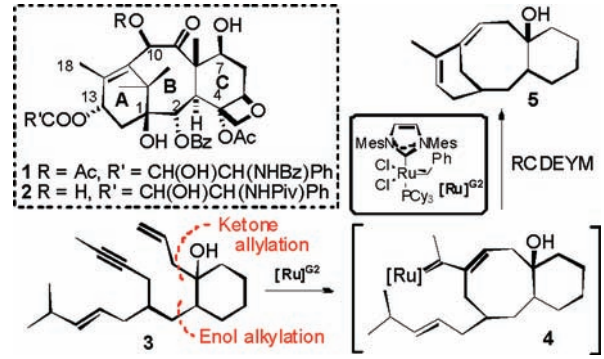
ABSTRACT



An efficient tandem ring-closing dienyne metathesis of dienynes derived from cyclohex-2-enone affords the [5.3.1] carbon framework characteristic of taxanes in a single-step process. Further stereoselective functionalizations of the resulting [5.3.1] carbon framework lead to an advanced intermediate in a novel synthetic strategy for taxane analogs.

The effective anticancer properties of some of the members of the taxane family for the treatment of several types of tumors still attract attention from chemists in terms of the synthesis of taxane derivatives.[1] Despite the relevant contribution of taxanes such as taxol **1** or taxotere **2** (Scheme 1) in improving the life quality and overall survival of cancer patients thanks to their unique mechanism of action,[2] the low solubility of these compounds in water, the appearance of several secondary effects, and the development of multidrug resistance (MDR)[3] represent serious limitations to their clinical use. Research in this area has therefore moved toward the preparation of less toxic analogs with improved properties.[1f] This search calls for new, efficient, and versatile synthetic methods for the construction and functionalization

Scheme 1



of the taxane skeleton. Unfortunately, the diverse range of methods developed to date to synthesize these polycyclic frameworks generally requires a large number of chemical transformations.[4]

Nowadays, not only must any new synthetic methods for the preparation of active compounds be designed bearing in mind the atom and step economy, but they should be benign

(1) For reviews on the clinical use of taxanes, see: (a) Rowinsky, E. K. *Annu. Rev. Med.* **1997**, *48*, 353. (b) Von Hoff, D. D. *Semin. Oncol.* **1997**, *24*, 3. (c) DeFuria, M. D. *Phytomedicine* **1997**, *4*, 273. (d) Eisenhauer, E. A.; Vermorken, J. B. *Drugs* **1998**, *55*, 5. (e) Crown, J.; O'Leary, M. *Lancet* **2000**, *335*, 1176. (f) Galletti, E.; Magnani, M.; Renzulli, M. L.; Botta, M. *ChemMedChem* **2007**, *2*, 920.

(2) (a) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. (b) Horwitz, S. B.; Davidson, M. W.; Holton, R. A. *Trends Pharmacol. Sci.* **1992**, *13*, 134. (c) Jordan, M. A. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 1.

(3) Krisna, R.; Mayer, L. D. *Eur. J. Pharm. Sci.* **2000**, *11*, 265.

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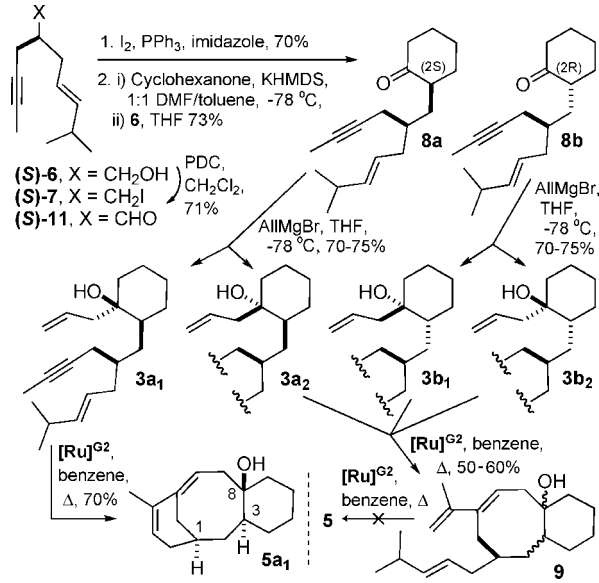
with respect to the environment and also be economically viable.[5] For these reasons, new methods must be developed and of special interest are the cascade reactions, which are rapidly gaining ground.[6] We recently reported ring-closing dienyne metathesis (RCDEYM)[7,8] applied to the synthesis of novel taxostereoids.[9] In this Letter we describe our initial studies into a highly efficient and stereoselective synthesis of an advanced taxane deriative starting from cyclohexenone.

We envisaged that the most rapid strategy to test the RCDEYM approach to taxane derivatives would be based on dienynes **3** (Scheme 1), which are available by enol alkylation followed by carbonyl allylation.[9] In the same way as other dienynic metatheses, the terminal isopropyl group in the enynic moiety of **3** would direct the initial incorporation of the ruthenium to the less-substituted double bond. Cyclization of this dienyne in such a way would provide the desired [5.3.1] framework (**5**) through the secondary vinylideneruthenium(II) intermediate **4**. The six-membered ring would not only represent the taxane C-ring but would also help to form the B-ring by acting as platform for the successive annelations.[10]

The enantiopure alcohol (*S*)-**6** (Scheme 2), prepared as described previously,[9b] was transformed into iodide (*S*)-**7** by

Scheme 2



treatment with iodine and triphenyphosphine. This compound was then reacted at −78 °C with the enolate of cyclohexanone, generated with potassium hexamethyldisilazide, to furnish the corresponding diastereomeric mixture (**8a** and **8b**) in a 1:1 ratio.[11] The two epimers were easily separated by flash chromatography and then treated separately with a solution of allyl magnesium bromide in THF at −78 °C to provide the corresponding four diastereomers (**3a**$_1$, **3a**$_2$ and **3b**$_1$, **3b**$_2$, respectively) in similar proportions.[11] Finally, each of the four dienynes was treated with 10% second generation Grubbs' catalyst **[Ru]**^{G2} under reflux in benzene for 2 h. Only one of the four isomers gave the [5.3.1] tricyclic compound (**5a**$_1$), while the other three isomers led to the formation of the trienes **9**, in which only the first annelation took place (Scheme 2). Additionally, none of the resulting triene derivatives **9** gave the tricycle **5** when subjected again to RCM with **[Ru]**^{G2}. This result confirms the importance of the geometry of the dienynic substrate, showing that only one of the diastereomers can undergo the double cyclization.

The relative stereochemistry of the tricycle **5a**$_1$ was proposed on the basis of theoretical calculations owing to the absence of characteristic signals in the ^{1}H NMR spectrum that could help to establish its structure.[12] Molecular mechanical calculations indicate that the lowest-energy isomer

(4) (a) 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. (b) Holton, R. A.; Somoza, C.; Kim, H. B.; Biediger, R. J.; Boatman, P. D.; Sindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C.; Bomnmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; 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. (e) Morihara, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980. (f) Mukaiyama, T.; Shima, I.; Iwadare, H.; Saitoh, M.; Nisimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tany, Y.-I.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

(5) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (c) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807. (d) Wender, P. A. *Tetrahedron* **2006**, *62*, 7505. (e) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(6) For reviews, see: (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1332. (b) Ho, L. L. *Tandem Organic Reactions*; Wiley: New York, 1992. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (f) McCarroll, A. J.; Walton, J. C. *Angew Chem., Int. Ed.* **2004**, *40*, 2224.

(7) For reviews on dienyne metathesis, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (b) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, p 176. (c) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (d) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (e) Diver, S. T.; Giessert, A. J. *Synthesis* **2004**, 466. (f) Maifeld, S. D.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118.

(8) For studies of the enyne ring-closing metathesis mechanism, see: (a) Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444. (b) García-Fandiño, R.; Castedo, L.; Granja, J. R.; Cárdenas, D. J. *Dalton Trans.* **2007**, 2925.

(9) (a) García-Fandiño, R.; Codesido, E. M.; Sobarzo-Sánchez, E.; Castedo, L.; Granja, J. R. *Org. Lett.* **2004**, *6*, 193. (b) Aldegunde, M. J.; García-Fandiño, R.; Castedo, L.; Granja, J. R. *Chem. Eur. J.* **2007**, *13*, 5135.

(10) (a) Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (b) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855. (c) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yand, J. *Org. Lett.* **2000**, *2*, 1259. (d) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742. (e) Bourgeois, D.; Pancrazi, A; Ricard, L. P.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726.

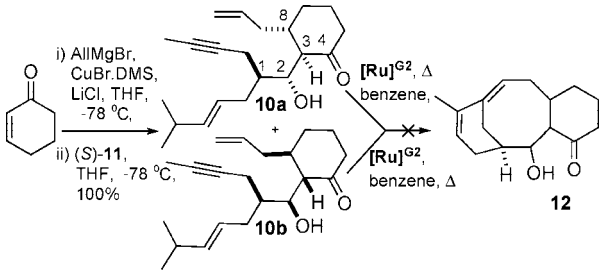
(11) The relative stereochemistry of the different intermediates in this manuscript was arbitrarily assigned at this point, but it was later confirmed by X-ray crystallography of an enantiomer of the monobenzoate of diol **15a**$_{4R}$ (see Figure 1, Supporting Information).

(12) It is known that the introduction of some sort of conformational constraint, such as rings or certain functional groups, facilitates the annelation of medium-sized carbocycles and that the *trans* disposition of the dienynic precursors further favors the cyclization of these types of rings. (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (b) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (c) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (d) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (f) Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301. For a short overview of the synthesis of medium-sized rings by RCM, see: (g) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

has a *trans*-fusion 6-8 bicyclic system and that H1 and H3 are both oriented to the same face (**5a$_1$**) (see Figure 2 in Supporting Information),[13] with this arrangement being 6.5−10.4 kcal/mol more stable than any other stereoisomers.

The results described above show the feasibility of the proposed strategy. However, in order to improve the preparation of the *trans*-isomer between allylic and enyne moieties and also to increase the structural complexity of the skeleton by introducing some of the pharmacophore-relevant functional groups present in the biologically active taxanes, a new strategy was designed based on cuprate addition to cyclohex-2-enone followed by trapping of the resulting enolate with aldehyde (*S*)-**11** (Scheme 3), with the new target being the hydroxylated dienyne **10**.

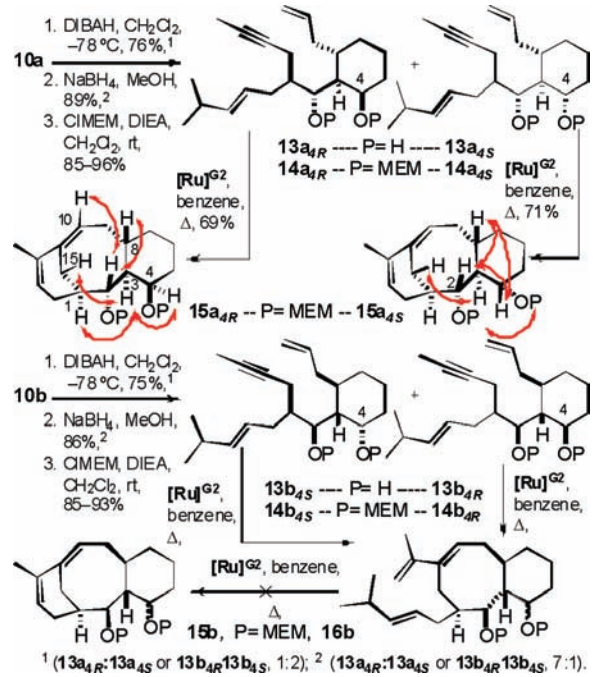
Scheme 3



According to this approach, cyclohexenone was treated with a freshly prepared allyl cuprate solution at −78 °C, and the resulting enolate was reacted with aldehyde (*S*)-**11** to afford a 1:1 mixture of the dienyne isomers (**10a** and **10b**). The stereochemistry assignment was based on the well-known *anti*-aldol selectivity and on the assumption that the *trans*-aldols were obtained (Scheme 3), though it was not possible at this point to confirm this proposal by NMR experiments.[14] Unfortunately, the hydroxyketones (**10a**, **10b**) were not transformed into the desired tricyclic compound **12** when subjected to metathesis conditions; instead, complete decomposition of the dienynes was observed.

To avoid this setback and after unsuccessful attempts to protect the carbonyl group as an acetal, we opted for a reduction. Treatment with diisobutylaluminum hydride (DIBAH) of both isomers separately afforded in each case the corresponding two isomers **13a$_{4R}$:13a$_{4S}$** and **13b$_{4R}$:13b$_{4S}$** (epimers at the taxol C4) in a 1:2 ratio, while treatment with sodium borohydride changed the ratio to 7:1 (Scheme 4).[11] The stereochemistry of this center is not important at this stage because the oxetane ring will be introduced later from either of the two C4-stereomers. Unfortunately, none

Scheme 4



of the resulting diols (**13**), when subjected to the metathesis conditions, led to the desired tetracyclic compound, with complete decomposition of the starting dienynes observed.[15] In view of the known instability of these diols, they were protected to give the corresponding products **14a** and **14b**, which were in turn subjected to previously optimized RCDEYM conditions (10% **[Ru]^{G2}**, benzene, Δ).[9b] After 1.5 h it was confirmed by TLC that dienynes **14a$_{4R}$** and **14a$_{4S}$** gave, in each case, one single product, visible by UV light, that was purified and unequivocally identified as the corresponding tricyclic systems **15a$_{4R}$** and **15a$_{4S}$**. A thorough inspection of the bidimensional spectra of these compounds enabled us to determine definitively most of the stereogenic centers. The NOE relationships in **15a$_{4R}$** between H1 and H3 and H3 and H15, coupled with the strong interaction between H2 and H8 and H10, can only be explained if, as expected, the polycyclic framework possesses the (3*S*-8*S*) *trans*-fusion, with an (*R*) configuration in C2, derived from the originally predicted *anti*-aldol condensation. Moreover, the NOE relationship between H3 and H4 suggests an (*R*) configuration for this latter center, meaning that the two hydroxy groups are in a *trans*-disposition. The 2D-spectra of **15a$_{4S}$** showed NOE interactions H3−H15, H3−H1, H2−H8, and H2−H10, which define the skeleton structure of these molecules. An NOE relationship between H4 and H8 and a weaker one between H4 and H2 were also observed, and these confirm the *cis*-disposition of the hydroxy groups.

On the other hand, dienynes **14b** reacted to afford a complex mixture of products in which the main isolated compound was identified as the respective triene derivative **16b** rather than the desired tricyclic products **15b**. Treatment of isolated **16b$_{4R}$**, again with catalyst **[Ru]^{G2}**, showed the

(13) The geometries were determined using the program Gaussian 98W. Frish, M. J. et al. *Gaussian 98, Revision A.5*; Gaussian, Inc.: Pittsburgh, PA, 1998.

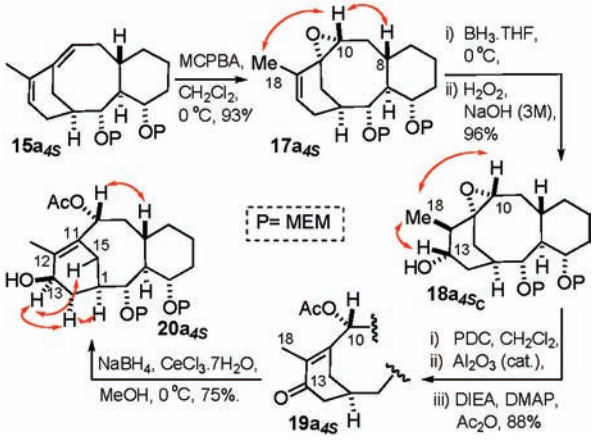
(14) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(15) 1,3-Diols have been claimed to decompose under metathesis conditions: (a) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444. (b) Kariuki, B. M.; Owton, W. M.; Percy, J. M.; Pintat, S.; Smith, C. A.; Spencer, N. S.; Thomas, A. C.; Watson, M. *Chem. Commun.* **2002**, 228.

formation of a more polar and UV-visible compound that could not be characterized due to rapid decomposition.[16]

Once we had studied the construction of the tricyclic frameworks, we decided to increase the complexity of **15a$_{4S}$**, the C4 stereochemistry of which corresponds to the taxol.[17] Treatment of **15a$_{4S}$** with 1 equiv of *m*-chloroperbenzoic acid yielded the epoxide **17a$_{4S}$** (Scheme 5), in which the oxirane

Scheme 5



has been formed at the most reactive olefin and the least hindered face, as confirmed by the NOEs observed between H8 and H10, and H10 and Me18. Hydroboration-oxidation of **17a$_{4S}$** furnished alcohol **18a$_{4S}$** in very good yield. Once again, the NOE relationships between H13-Me18 and Me18-H10 indicate that the attack of the borane took place at the α-face of the taxane skeleton. Oxidation of **18a$_{4S}$** with PDC was followed by treatment of the resulting ketone with a catalytic amount of Al_2O_3 to facilitate ketone enolization that induces epoxide opening while forming the double bond between C11 and C12. Trapping of the resulting alkoxide with acetic anhydride gave compound **19a$_{4S}$** in excellent yield. Finally, reduction of **19a$_{4S}$** under typical Luche conditions[18] provided alcohol **20a$_{4S}$** as a single diastereomer. The strong NOE interaction between H8 and H10 corroborates the expected 10-(*R*) configuration, and the NOEs observed between H13 and H15 and H13 and H14 confirm a 13-(*R*) configuration.

In summary, we have successfully used the cascade ring-closing dienyne metathesis (RCDEYM) to prepare the bicyclo[5.3.1]undecadiene taxane carbon system, including the C2,C4-hydroxy groups and the methyl Me18, which is characteristic of taxol, from simple dienynes containing a six-membered ring that acts as a platform for the double cyclization. We can conclude from our experiments that the cascade cyclization takes place only if the stereocenters C1 and C3 match to give the tetracyclic framework in which its substituents (H in this case) are oriented toward the same face. We also carried out initial studies aimed at introducing additional functional groups on the taxane skeleton, developing a fairly short synthetic route to introduce the characteristic acetate at C10 and a hydroxyl group at C13, which would readily allow the coupling of the amino acid side chain. Further studies aimed at different kinds of taxane analogs and related biological studies are currently underway.

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Supporting Information Available: Figures 1SI, 2SI, 3SI and Scheme 1SI together with detailed descriptions of the synthesis of the key compounds and their complete characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In order to understand better the different behavior of dienynes **14a** and **14b**, we performed the energetic minimization of the four possible tricyclic derivatives, assuming as mentioned before that the **b** isomers have the *trans* fusion opposite to the **a** ones. We found that the theoretical calculations[13] predict a gap of 20 kcal/mol between **15a** isomers (3*S*,8*S*-products) and the (3*R*,8*R*)-**15b**-ones, which would explain the low stability of the latter and the great difficulty in forming them; see Figure 3 in Supporting Information.

(17) Same synthetic squence was followed with isomer **15a$_{4R}$** to give taxane **20a$_{4R}$**; see Scheme 1 in Supporting Information.

(18) Germal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.