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Synthesis of 2-Ene-1,4-diols by a New Cascade-Opening of 1,3-Diepoxides: Towards an Efficient Synthesis of Dihydroxytaxoid Derivatives

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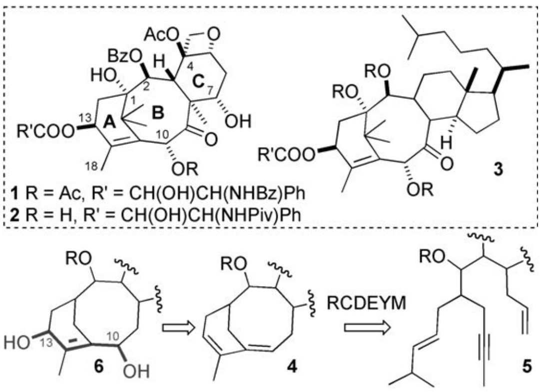
Dedicated to Professor Josep Font on the occasion of his 70th birthday

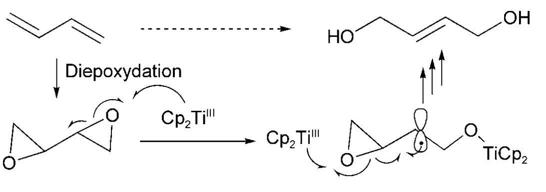
The impressive anticancer properties of some taxane-family members make these molecules and their derivatives attractive targets for chemical synthesis.[1] Despite the relevant contribution of taxanes, such as taxol **1** or taxotere **2** (Scheme 1), advances still are needed to improve their properties by looking for less toxic analogues with improved properties.[1f] In the last few years, our research group has been involved in the development of new taxane analogues[2] and taxosteroids **3**.[3] Their framework (**4**) was prepared through a cascade ring-closing dienyne metathesis (RCDEYM) reaction from dienyne **5** (Scheme 1).[4] Herein, we report the transformation of derivatives **4** into taxane-diols **6** by way of a new and general strategy.



Scheme 1. Taxanes, such as taxol (**1**) and taxotere (**2**), and taxosteroid structures (**3**) and proposed synthetic scheme for taxane like derivatives **6** from dienyne **5**.

Few methods are known for the regio- and stereoselective 1,4-addition of oxygen functions to conjugated dienes.[5–9] Moreover, they are rarely successful with dienes that normally do not adopt the s-*cis* conformation or when the substrate possesses a constrained structure that does not allow the formation of the π-allyl complex.

Having failed to prepare the alk-2-ene-1,4-diol moiety (**6**) from the diene derivatives of type **4** under the reported conditions,[7–10] we decided to study other alternatives. We envisaged that titanocene(III) chloride could be useful in the construction of the alk-2-ene-1,4-diol system from diepoxides derived from 1,3-dienes (Scheme 2).[11–14] The titanium complex would react with the oxacyclopropane rings to generate a β-titanoxy radical, which could then trigger the second epoxide opening to give the alk-2-ene-1,4-diol moiety.



Scheme 2. General approach proposed for the preparation of enediols by radical diepoxide opening.

Thus, taxosteroids **7a** and **7b** (Scheme 3) were transformed into the corresponding dioxiranes (**8** and **9**) using 3-chloroperoxybenzoic acid (*m*CPBA). When the 4:1 inseparable mixture of dioxiranes **8a**/**9a** was treated with a freshly prepared solution of titanocene(III) chloride[15] only the major isomer reacted to give a new compound, which was identified as the *cis*-**10a** based on its 1D- and 2D-NMR spectra, while the other isomer remained unaltered. Similarly, when we carried out the reaction on pure diepoxides **8b**

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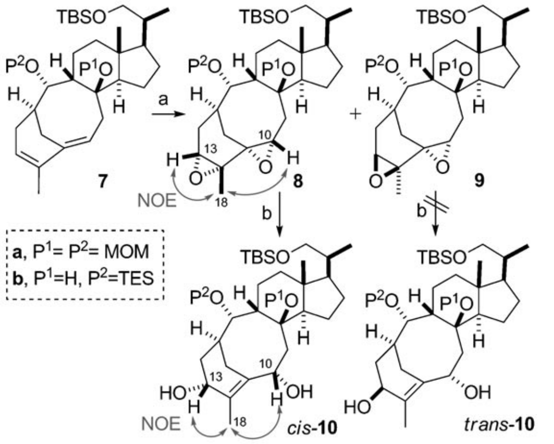
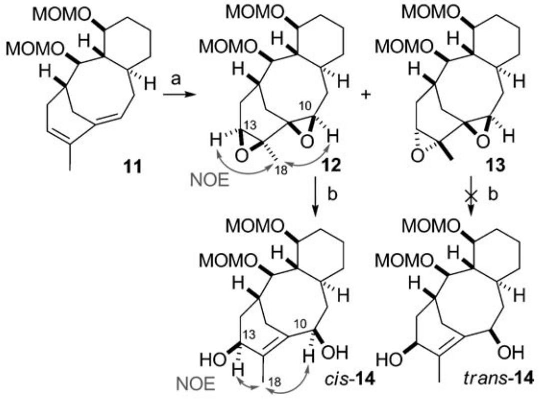


Scheme 3. a) *m*CPBA, CH_2Cl_2, 0 °C, 71 % for **8a/9a** (4:1) and 85 % for **8b/9b** (15:1); b) $[TiCl_2Cp_2]$, Zn, THF, 0 °C.

and **9b**, only the major isomer (**8b**) reacted, even in the presence of the unprotected hydroxyl group ($P^1 = H$), to provide *cis*-**10b** in excellent yield.

In the same way, we subjected separately diepoxides **12** and **13** (Scheme 4), derived from taxane **11**, to the same conditions. Once again, only isomer **12** underwent the double oxirane opening to give diol *cis*-**14** (92 %). These results clearly open the opportunity to efficiently prepare novel taxane derivatives starting from simple cyclohexenones through RCDEYM,[2] followed by appropriate functionalization of the diols resulting from diepoxide opening.

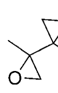
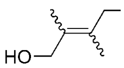
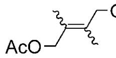
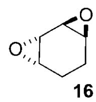
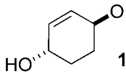
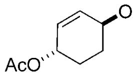
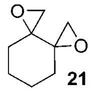
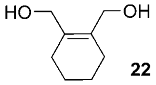
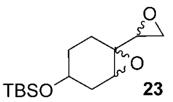
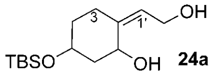
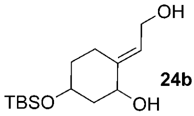


Scheme 4. a) *m*CPBA, CH_2Cl_2, 0 °C, 81 % for **12/13** (5:1); b) $[TiCl_2Cp_2]$, Zn, THF, 0 °C, 92 % for *cis*-**14**.

These results could be mechanistically explained, as shown in general form in Scheme 2, in terms of a titanium-induced sequential oxirane opening of diepoxide moiety involving the initial formation of an α-epoxy methinyl radical.[11,13,16] Epoxide opening is more likely to take place on the C12–C13 oxirane, because the alternative opening of the epoxide at C10–C11 would result in the formation of a bridgehead radical intermediate. The lack of reactivity of the *trans*-diepoxide isomers (**9** and **13**) in comparison with the *cis*-diepoxides (**8** and **12**) can be explained in terms of the steric hinderance provided by the taxane skeleton, which somewhat restricts the epoxide accessibility to the titanium complex, and thus they are recovered unchanged.

The above promising results encouraged us to further explore the scope of this methodology with simple substrates (Table 1). The first experiments with epoxides **15** and **16** (entries 1 and 3) gave the corresponding alkenediols (**17** and **19**) as single stereoisomers but in very low yield,[16] which was attributed to their isolation difficulties associated to their low molecular weight and polarity. This was partially confirmed when compounds **17** and **19** were transformed in situ into the corresponding diacetates **18** and **20** (entries 2 and 4) with a notable increase of isolated yields. Interestingly, the *trans*-diepoxide **16**[16] can evolve into the corresponding *trans*-enediol, probably because there is reduced geometrical bias for the radical intermediate to adopt the sp^2 hybridization that evolves into the olefin. Better results were obtained with diepoxide **21** (entry 5), giving the enediol **22** in good yield. Subjecting an inseparable diasteromeric mixture of dioxiranes **23** (see Scheme 1SI in supporting information for its synthetic preparation scheme)[17] to the Ti^{III} conditions provided a 2:1 mixture of alkenediols **24a** and **24b** (entry 6) in very good yield. The results described above prove the validity of the proposed strategy for the preparation of 2-alkene-1,4-diols from conjugated dienes/

Table 1. Studies for the transformation of diepoxides into alkenediols.

Entry	Diepoxide	Product	Yield[a]
1	 **15**	 **17**	16[b]
2		 **18**	30[c]
3	 **16**	 **19**	21[b]
4		 **20**[d]	51[c]
5[b]	 **21**	 **22**	69
6[b]	 **23**	 **24a**[e]  **24b**[e]	89

[a] Isolated yields. In the case of entries 2 and 4 the yields are for the two steps. [b] Reaction conditions: 0.05 M in THF, $[\{TiClCp_2\}_2]$ (0.2 M in THF, 1 equiv), 0 °C. [c] i) 0.05 M in THF, $[\{TiClCp_2\}_2]$ (0.2 M in THF, 1 equiv), 0 °C; ii) Ac_2O, DIEA, DMAP, RT. [d] Diacetate **20**, and consequently its precursor **19**, were identified as the *trans* isomers by comparison of its spectroscopic data with those previously reported.[16] [e] Compound **24a** was assigned the *Z* configuration on the basis of the NOE between H1′ (5.52 ppm) and H3 (2.14 ppm). Consequently, the *E* configuration was assigned to the other isomer (**24b**).

diepoxides through the radical induced oxirane ring opening.

In summary, we have successfully functionalized the constrained 1,3-olefin system of taxane and taxosteroids frameworks **4** to the dihydroxylated analogues by means of a new method that relies on olefin diepoxidations followed by radical opening of the dioxirane system with titanocene(III) chloride. This methodology has also been extended to other substrates confirming the general validity of this methodology. Further studies to determine the scope and limitations of this process are currently underway.

Experimental Section

Zinc dust (196 mg, 3 mmol) was added to a solution of [TiCl$_2$Cp$_2$] (249.5 mg, 1 mmol) in THF (2.5 mL) and the suspension was vigorously stirred for 1 h under Ar atmosphere. This freshly prepared solution of [{TiClCp$_2$}$_2$] (0.2 M, 0.6 mL, 0.13 mmol) was added dropwise to a solution of the inseparable mixture of diepoxides **8a/9a** (25 mg, 0.042 mmol) in THF (2.5 mL) at 0 °C and the mixture was stirred at the same temperature. After 1 h, HCl (1 M) was added and the aqueous layer was extracted with Et$_2$O, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was subjected to flash chromatography (90% AcOEt/hexanes) to yield diol *cis*-**10a** (21 mg, 81%, $R_f=0.2$ (100% AcOEt), white solid).

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