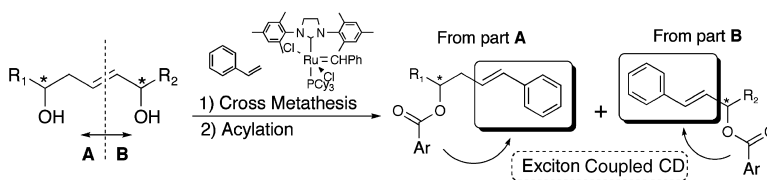## Communication

Absolute Stereochemistry of Allylic Alcohols, Amines, and Other Ene Moieties: A Microscale Cross Metathesis/Exciton Chirality Protocol

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Absolute Stereochemistry of Allylic Alcohols, Amines, and Other Ene Moieties: A Microscale Cross Metathesis/Exciton Chirality Protocol

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Many natural products with allylic alcohol moieties have recently been reported, for example, haliclonyne, pellynic acid, clathrin B, xenicane diterpene, and arenosclerin A.[1] The circular dichroic (CD) exciton chirality method based on the coupled oscillator theory has been used for determining the absolute configurations of various organic compounds.[2] In the case of allylic alcohols,[3-5] their absolute configurations are determined by conversion into allylic benzoates ("allylic benzoate method").[3] The allylic hydroxyl is converted into an unsubstituted benzoate, λ_{max} ca. 230 nm (^1L_a band, ϵ 15 300), or p-bromobenzoate, λ_{max} ca. 244 nm (^1L_a band, ϵ 19 500), with absorption maxima close to that of the double bond at ca. 195 nm (π, π^* transition, ϵ 12 000).[3] Recently, the 2-naphthoate chromophore with an intense ^1B_b band at 230 nm (ϵ 130 000) has been used; this chromophore couples with the double bond to yield a Cotton effect (CE) severalfold more intense than that of the corresponding unsubstituted benzoate.[6] Allylic amines have also been examined by conversion of primary amino groups into phthalimides (λ_{max} 220 nm, ϵ 36 000).[7]

The configurations of allylic benzoates, naphthoates, or phthalimides have mostly been assigned only from the sign of the longer wavelength CE instead of the entire couplet, because the shorter wavelength wing arising from the double bond moiety below 200 nm is difficult to measure.[8] Under favorable cases, it is possible to detect both wings, which become more pronounced in the difference CD before and after benzoylation.[8] However, when other intense chromophores exist in the vicinity of the allylic acylate, the configurational assignment becomes unreliable or even erroneous; for example, the method is not applicable to 1-indenol.[9] In the case of archangelolide, the absorption of its allylic α,β-unsaturated ester overlaps with that of the existing γ-lactone ring; subtraction of the CD of the corresponding saturated ester clarified the longer wavelength wing of the weak couplet and established its absolute configuration.[4]

A more general protocol that overcomes the restriction of conventional methods, the accessibility of only one wing or the relatively weak CD couplet, becomes desirable. We report here a microscale method where the double bond is converted into a styrene, λ_{max} 248 nm (ϵ 15 000), or other styrenoid chromophores by cross olefin metathesis.[10,11] The recently developed Grubbs' Ru catalyst 1[12] was applied because of its efficient transformation under mild conditions that do not cause epimerization of the substrates. The styrenoid chromophore then couples with the allylic acylate or a preexisting chromophore to yield a distinct couplet.

Prostaglandin A_1 ethyl ester (PGA$_1$) was chosen as a model for the allylic alcohol (Scheme 1). Because PGA$_1$ bears an intense CD Cotton effect at 231 nm ($\Delta\epsilon$ +19.2) due to the twisted enone chromophore,[13] the allylic benzoate method is not applicable. Furthermore, acylation attempts led to a mixture of unidentified products arising from the instability of PGA under basic conditions. According to the new protocol, PGA$_1$, 100 μg, was reacted with excess styrene in the presence of Grubbs' catalyst 1 (Scheme 1).

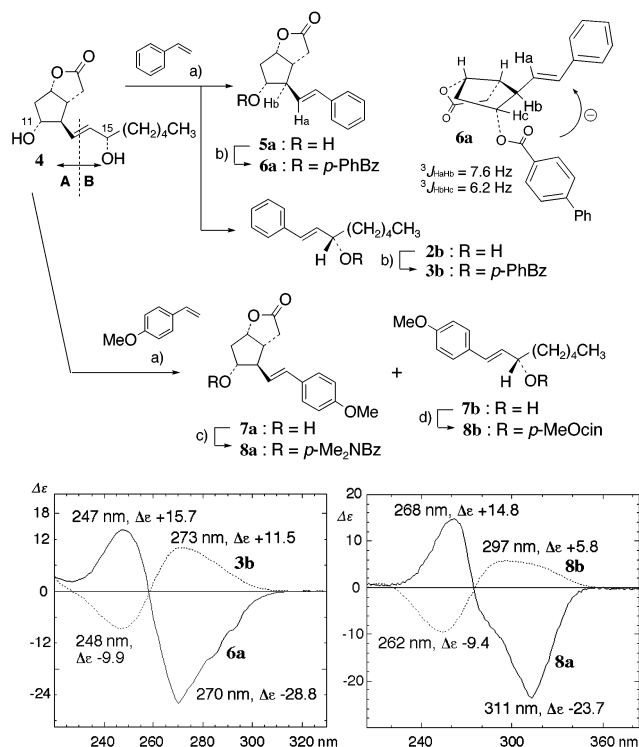**Scheme 1.** Derivatization of Prostaglandin A$_1$ to Styrenoids[a]
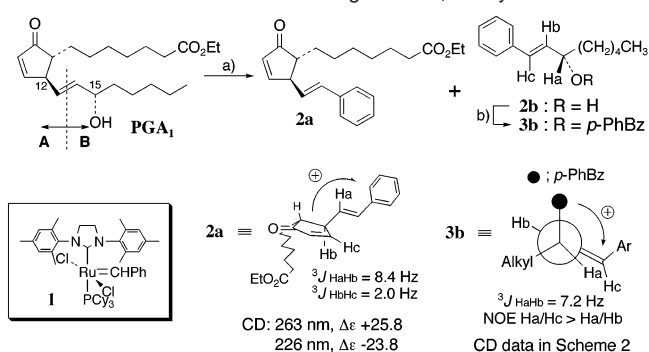
[a] Conditions: (a) 10 equiv of styrene, 10 mol % of Grubbs' catalyst 1, CH$_2$Cl$_2$, 40 °C, 85% for 2a, 89% for 2b; (b) p-phenylbenzoic acid, EDC, DMAP, CH$_2$Cl$_2$, room temperature, 80%; CD and NMR spectra in MeCN (similar CD in CHCl$_3$ (Supporting Information)).

Moieties A and B of PGA$_1$ were converted into (E)-styrenoids 2a and 2b under mild conditions. Acylation of 2b with p-phenylbenzoic acid, λ_{max} 270 nm (ϵ 20 700),[2] gave 3b, the NMR and the computational analysis of which disclosed the most stable conformer (Scheme 1).[14] In agreement with the known chirality of 3b, the coupling between the p-phenylbenzoate and styrene showed the expected positive CD couplet. Moreover, the preexisting enone moiety in part A also serves as one of the coupled chromophores in 2a; the positive couplet arising from the enone and styrenoid chromophore coupling[13,15] agrees with its known stereochemistry (conformation as deduced from $^3J_{HH}$ values shown in Scheme 1). This microscale method thus establishes the absolute stereochemistry of PGA$_1$ or that of both moieties A and B, a determination that would not be straightforward by other methods.

"Corey-lactone" 4 carries C-11 homoallylic and C-15 allylic hydroxyls (Scheme 2). The monobenzoates of C-11 and C-15 hydroxyls in 4 both exhibited weak CEs at ca. 230 nm, but the counterparts were unclear because of overlap with the intense lactone CD (see Supporting Information).[5a] On the other hand, the CD couplet of 4 dibenzoate showed a negative CE at 235 nm, but the positive counterpart expected at ca. 220 nm was again obscured by the lactone chromophore. Moreover, a prerequisite for determination of the absolute configuration of 4 from its dibenzoate CD would be the nontrivial establishment of the C-11 to C-15 conformation under conditions of CD measurements.

For prostanoid 4, the double bond was therefore reacted with styrene in the presence of catalyst 1 to give styryl alcohols 5a and 2b, readily separable (Scheme 2). p-Phenylbenzoylation yielded 6a and 3b, the conformation of the former being deduced from the $^3J_{HH}$ values. Their CDs exhibited the expected negative and positive couplets between the p-phenylbenzoate and styrene chromophores, respectively. The extrema were sufficiently far from the lactone absorption, λ_{max} ca. 200 nm, so that there was no interference. It is to be noted that the cross metathesis and acylation two-step

Scheme 2. Derivatization of **4** to Styrenoids[a]

Scheme 3. Derivatization of Allylic Amine to Styrenoids[a]

[a] Conditions: (a) 2,3-naphthoic acid anhydride, pyridine, 80 °C, 81%; (b) 10 equiv of styrenes, 10 mol % of Grubbs' catalyst **1**, CH₂Cl₂, 40 °C, 84% for **10a**, 61% for **10b**; CD and NMR spectra in MeCN.

as the enone moiety shown in Scheme 1. Absolute configurational studies of natural and synthetic compounds with various double bond substitution patterns, with and without extra chromophores, are ongoing.

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Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

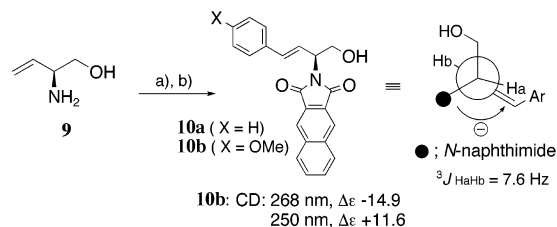[a] Conditions: (a) 10 mol % of catalyst **1**, CH₂Cl₂, 40 °C, 66% for **5a**, 63% for **2b**, 61% for **7a**, 73% for **7b**; (b) p-phenylbenzoic acid, EDC, DMAP, CH₂Cl₂, room temperature, quant. for **6a**; (c) p-dimethylaminobenzoylimidazole, DBU, MeCN, room temperature, 89; (d) p-methoxycinnamic acid, EDC, DMAP, CH₂Cl₂, room temperature, 92%; CD and NMR spectra in MeCN.

sequence is performed in one pot without isolation of the intermediate, and if needed it can be scaled down to 10 μg of sample, which is much less than that required in the Mosher ester method.

Various p-substituted styrenoids can be used to replace the C=C double bond so that the exciton analysis is performed at more bathochromic regions to avoid interference from other preexisting chromophores, if any. Thus, the double bond in prostanoid **4** was replaced with a p-methoxystyrenoid, λ_{max} 259 nm (ϵ 19 200), by reacting with p-methoxystyrene to give styrenoids **7a** and **7b**. p-Methoxystyrenoid **7a** was acylated to its dimethylaminobenzoate **8a**, λ_{max} 307 nm (ϵ 28 200), while **7b** was converted into its p-methoxycinnamate **8b**, λ_{max} ca. 300 nm (ϵ 23 400).[2] The CD couplets are now shifted to a more red-shifted region than those of **6a** and **3b** (Scheme 2).

The method is also applicable to allylic amines (Scheme 3). The primary amino group of chiral amine, (R)-**9**, was converted into its naphthimide, λ_{max} 258 nm (ϵ 64 000).[2] The cross metathesis with styrene or p-methoxystyrene provided the corresponding styrenoid compounds **10a**–**b**, which showed the expected negative exciton couplets reflecting its absolute stereochemistry.

In summary, a microscale cross metathesis/exciton chirality protocol for the determination of absolute configurations of allylic alcohols, amines, and related systems has been developed. The method is applicable to molecules carrying, in addition to the allylic hydroxyl and amino groups, various preexisting chromophores such

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(14) The most stable conformer found by MC/MM3 calculation has Ha/Hb almost *anti*-periplanar with a dihedral angle θ = 173° and $^3J_{HaHb}$ = ca. 10 Hz according to the Karplus equation. Consideration of all conformers <2 kcal mol⁻¹ and Boltzmann distribution leads to an average calcd $^3J_{HaHb}$ of 8.8 Hz; this differs by ~1.6 Hz from the exptl $^3J_{HaHb}$ of 7.2 Hz. This difference is most likely due to electronegative effects of styrene and benzoate moieties attached to the vicinal carbons. Relative NOE Ha/Hc > Ha/Hb also supports the preferred *anti*-periplanar conformation of **3b** shown in Scheme 1.
(15) The cyclopentenone CE of PGA₁ was subtracted to obtain a clearer couplet.

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