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, haliclonyme, pellynic acid, clathrin B, xenicanne diterpene, and arenosclerin A. 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. In the case of allylic alcohols, their absolute configurations are determined by conversion into allylic benzoates (“allylic benzoate method”). The allylic hydroxyl is converted into an unsubstituted benzoate, \( \lambda_{\text{max}} \) ca. 230 nm (1L\( \alpha \) band, 15 300), or \( p \)-bromobenzoate, \( \lambda_{\text{max}} \) ca. 244 nm (1L\( \alpha \) band, 19 500), with absorption maxima close to that of the double bond at ca. 195 nm (\( \pi, \pi^* \) transition, 12 000). Recently, the 2-naphthoate chromophore with an intense 1\( B\) \( \beta \) band at 230 nm (1L\( \alpha \) band, 19 500), with \( \lambda_{\text{ext}} \) ca. 230 nm (1L\( \alpha \) band, 19 500), was reacted with a \( p \)-PhBz acid, 89% for 2b, 89% for 2b. (b) \( p \)-Phenylobenzoic 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 \( p \)-Phenylobenzoic acid, \( \lambda_{\text{max}} \) 270 nm (\( \pi \) 20 700), gave 3b, the NMR and the computational analysis of which disclosed the most stable conformer (Scheme 1). In agreement with the known chirality of 3b, the coupling between the \( p \)-Phenylobenzoate and styrene showed the expected positive CD couplet. More recently, 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 agrees with its known stereochemistry (conformation as deduced from 3\( J_{\text{HH}} \) 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). 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 prostaglandin 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). \( p \)-Phenylobenzooylation yielded 6a and 3b, the conformation of the former being deduced from the 3\( J_{\text{HH}} \) values. Their CDs exhibited the expected negative and positive coupllets between the \( p \)-Phenylobenzoate and styrene chromophores, respectively. The extrema were sufficiently far from the lactone absorption, \( \lambda_{\text{max}} \) ca. 200 nm, so that there was no interference. It is to be noted that the cross metathesis and acylation two-step
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 6a is much less than that required in the Mosher ester method. The method is also applicable to allylic amines (Scheme 3).

The method is also applicable to allylic amines (Scheme 3). The primary amino group of chiral amine, (R)-9, was converted into its naphthimide, \( \lambda_{\text{max}} 258 \text{ nm (} \epsilon 64 000) \). The cross metathesis with styrene or p-methoxystyrene provided the corresponding styrenoid compounds 10a–h, which showed the expected negative exciton couplings 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 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.

References

14. (a) The most stable conformer found by MC/MM3 calculation has Ha/Hb almost anti-parallel with a dihedral angle \( \theta = 173^\circ \) and \( \psi_{\text{Ha}} = -6.4 \text{ kcal mol}^{-1} \). (b) The CD and NMR spectra in MeCN.
15. The cyclopentenone CE of PGA was subtracted to obtain a clearer couplet.

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