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The Proline and β-Lactoglobulin Mediated Asymmetric Self-Condensation of β-Ionylideneacetaldehyde, Retinal and Related Compounds.

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Abstract. Proline was found to effectively mediate the asymmetric reaction of β-ionylideneacetaldehyde **1A**, retinal and related α,β-unsaturated aldehydes to form their corresponding self-condensation products in reasonable enantiomeric excess (up to 65% ee). This same interesting conversion was also observed when **1A** was incubated in the presence of the milk whey protein β-lactoglobulin (BLG).

During the course of a recent photochemical investigation of retinal and its derivatives in the presence of the milk whey protein β-lactoglobulin, BLG,[1] we observed that one of the substrates, β-ionylideneacetaldehyde **1A**, underwent an entirely unexpected partial transformation to a new product which we describe herein. While the overall conversion to this previously unreported self-condensation product **2A** was relatively poor (*ca.* 11%), the reaction was clearly protein mediated as shown by its circular dichroism (Figure 1). In that this protein mediated chemical transformation has never before been reported, we set out to define some of the factors that govern this interesting conversion.[2]

Aldehyde **2A**, a yellow oil (λ_{max} = 360 nm in hexane), has a molecular ion corresponding to $C_{30}H_{42}O$ (HRMS: 418.325, calcd 418.324). Its ^{13}C-nmr spectrum[3] exhibits a single carbonyl, 12 olefinic and 17 sp^3 carbons. Its ^{1}H-nmr spectrum[4] exhibits the following readily identifiable features: an aldehyde singlet, three sets of coupled vinyl hydrogens (AB quartets), an AB quartet for the diastereotopic methylene hydrogens, two allylic methylenes and seven methyl singlets (two vinylic and five additional ones at higher field). Non-equivalence in the geminal dimethyl groups of both trimethylcyclohexenyl rings is attributable to their proximity to the chiral center at C_6 of the newly created ring as has been previously reported in similar systems.[5a,b]

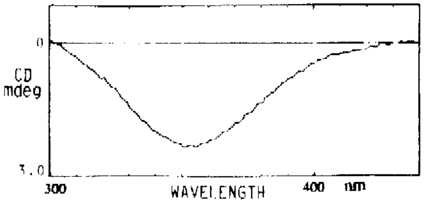
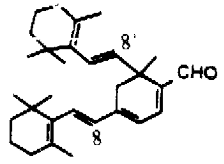
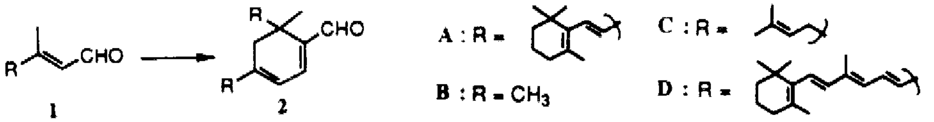


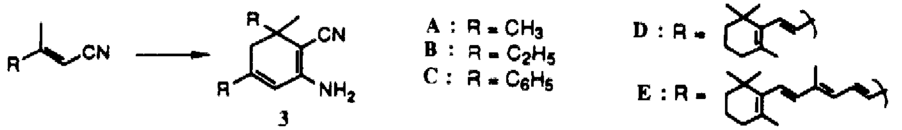
Figure 1. CD spectrum of **2A**.



2A

The base-catalyzed self-condensation of α,β-unsaturated aldehydes to form 1,3-cyclohexadienals is well documented. Thus, senecioaldehyde and citral (**1B, C**) afford the dimers **2B** and **2C**, respectively.[6a,b] Similarly, senecionitrile and related α,β-unsaturated nitriles can be induced to self-condense only under strongly basic conditions (e.g., LDA) to give the corresponding 2-amino-1,3-cyclohexadienenitriles **3A-C**.[7] Under the same conditions we discovered that dimers **3D** and **3E** could be obtained from β-ionylideneacetonitrile and retinonitrile, respectively.[8] For aldehyde **1A**, treatment with base (LDA, ethanolic KOH or piperidine), however, failed to produce any of the requisite dimer **2A**.





Secondary ammonium carboxylates are known to catalyze the aldol reaction. For example, a series of trifluoromethylated analogs of retinal were prepared by the piperidinium acetate-catalyzed condensation of trifluoroacetone with representative aldehydes.[9] When this reaction was repeated using **1A**, only a partial conversion (50%) to **2A** was realized.

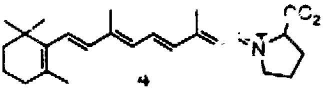
The biomimetic asymmetic cyclization of citral to optically active α-cyclocitral was effected by Yamada and co-workers in modest isolated and optical yield (4-26% and up to 33%, respectively) using a number of chiral pyrrolidine derivatives,[10] with no mention of any self-condensation products. We, therefore, turned our attention to the use of L-proline as the chiral auxiliary, widely used to effect a variety of asymmetric transformations (e.g., the synthetically important Wieland-Miescher ketone[11a] in high optical purity).[11b]

Quite gratifyingly, we found that upon treatment of **1A** with ethanolic L-proline (2 equivalents, 24h, RT) the optically active dimer **2A** ($[\alpha]_D$ = -239 +/- 1, *c* .201g, hexane) was obtained as the sole product in 52% isolated yield. This synthetic material exhibited a CD maxima essentially identical to the dimer obtained from **1A** in the presence of β-lactoglobulin.

The enantiomeric ratio for **2A** was 1 : 4.67 (65% ee) as determined by nmr spectroscopy (500 MHz) using the chiral lanthanide shift reagent, $Pr(hfc)_3$. Only partial peak resolution was observed for both the aldehydic proton and the vinylic proton, H_8', on the β-ionyl side chain at C_6 while one of the diastereotopic hydrogens, (presumably closest to the shift reagent) on the cyclohexadienyl ring, was clearly resolved.

Aldehyde **2A** was also converted to its diasteromeric menthylhydrazone derivative[12a,b] and readily separated by preparative hplc (Dynamax Microsorb, 20% ether in hexane) into its optically pure forms with retention times of 22 and 25 min and in 2.5 : 1 diastereomeric ratio, respectively. The optical yield of the menthylhydrazones could also be determined by nmr spectroscopy since the doublet for H_8, the vinylic hydrogen on the β-ionyl side chain proximal to the chiral center, was relatively well resolved for the individual diastereomers.

This transformation could also be effected with *trans*-4-hydroxy-L-proline or D-proline and *cis*-4-hydroxy-D-proline, with the opposite enantiomer predominating in the latter two cases. With Trp, His, Arg, Gly and Ileu, the self-condensation reaction of **1A** either failed or proceeded to a lesser extent than with Pro.



4

The general nature of the proline-mediated self-condensation reaction of α,β-unsaturated aldehydes was confirmed using senecioaldehyde, citral and retinal (**1B-D**). Interestingly, with retinal, treatment with proline in ethanol gave rise to the surprisingly stable protonated Schiff base, retinylidenylprolinium carboxylate **4**, previously characterized by nmr spectroscopy.[13] Only upon the addition of triethylamine could the PSB salt **4** be induced to self-condense to form the C_{40}-aldehyde **2D** as the sole product (76% yield, enantiomeric ratio = 2 : 1).[14] Subsequently, we observed that the presence of triethylamine at the onset accelerated the reaction for both citral and retinal (**1C,D**).

In conclusion, we have demonstrated that the amino acid proline effectively mediates the asymmetric self-condensation of a number of α,β-unsaturated aldehydes to generate cleanly chiral products in good isolated yield as well as reasonable optical purity. Both the scope and mechanism of this novel transformation as well as its possible applications in other naturally occurring systems are currently under investigation.[15]

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3. Noise decoupled ^{13}C-nmr (CDCl$_3$): δ 192.3, 144.7, 144.4, 141.5, 137.5, 137.4, 137.2, 133.8, 131.6, 131.4, 127.6, 124.6, 121.6, 39.5, 39.2, 38.5, 37.8, 34.3, 34.0, 33.1, 32.4, 28.93, 28.90, 28.57, 28.56, 25.0, 21.7, 21.1., 19.3 and 19.1 ppm.
4. ^{1}H-nmr (CDCl$_3$): δ 9.49 (s, 1H), 6.84 (d, J = 6.0 Hz, 1H), 6.09 (d, J = 6.0 Hz, 1H), 6.53 (d, J = 16.2 Hz, 1H), 6.21 (d, J = 16.2 Hz, 1H), 5.65 (d, J = 16.2 Hz, 1H), 5.35 (d, J = 16.2 Hz, 1H), 2.67 (d, J = 17.0 Hz, 1H), 2.39 (d, J = 17.0 Hz, 1H), 2.03 (t, J = 5.7 Hz, 2H), 1.90 (t, J = 5.7 Hz, 2H), 1.71 (s, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H) and 1.35-1.66 (m, 8H) ppm.
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8. The ^{1}H-, ^{13}C-nmr and COSY spectra for aminonitriles **3D** and **3E** were entirely consistent with the assigned structures (courtesy of D. Mead and W. Niemczura of this department).
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14. The uv-vis absorption spectrum of **4**, previously unreported, exhibited a λ_{max} at 455 nm in ethanol while its self-condensation product, C$_{40}$-aldehyde **2D**, had λ_{max} at 287 and 430 nm of equal intensity.
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