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Proline Promoted Synthesis of Ring-Fused Homodimers: Self-Condensation of α,β-Unsaturated Aldehydes†

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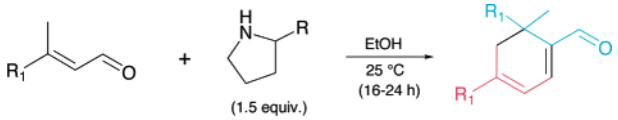

1,2,4-Trisubstituted cyclohexadienals can be prepared synthetically by self-condensation of β-methyl substituted α,β-unsaturated aldehydes. While molecules with this structural scaffold have been observed in nature, the biological roles of these compounds have yet to be thoroughly investigated. Here we investigate the use of L-proline and its derivatives to effect synthesis of these ring-fused homodimers. The scope of this reaction is investigated with different substrates and proline derivatives. Mechanistic hypotheses are put forth supported by NMR and mass spectrometry studies. The method will enable diversification of this scaffold in sufficient quantities for biological investigations.

Introduction

Carotenoids form an important class of biologically active molecules and play a critical role in energy transfer processes such as photosynthesis or photoprotection. In animals, carotenoid metabolites, e.g., retinoids, serve as chromophores for the visual signal transduction systems.[1]

Interestingly, condensation of all-*E*-retinal gives a C-40 ring-fused dimer **1a** (Figure 1) (with a cyclohexadienal structural core) that has been implicated as a contributor of age-related macular degeneration, the leading cause of blindness in the elderly.[2] While molecules with this structural scaffold are not unprecedented in nature, considerably less is known regarding the biological functions of these molecules. The self-dimerization of citral, for example, has been suspected since the late 1890s.[3] The 1,2,4-trisubstituted structure (**1i**) was definitively ascribed in 1932.[4] Recently, citral dimer **1i** was isolated from the North Sea bryozoan *Flustra foliacea*[5] and shown to exhibit antibacterial activity against *Roseobacter sp.* and *Sulfitobacter sp.* in an agar diffusion assay (100 μg resulted in a 0.5 and 1.0 cm zone of inhibition).[6]

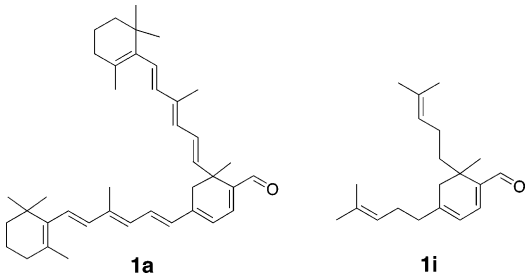

FIGURE 1. Structures of retinal (**1a**) and citral (**1i**) self-condensation products.

Over the past century, a variety of conditions have been employed to develop facile routes to these self-condensation products. The general synthetic strategy has involved the use of strongly basic conditions such as lithium diisopropyl amide (LDA),[7] sodium hydride (NaH),[8] potassium hydride (KH),[2,3,9]

† A provisional patent on this work is in place (13260-P011V1) on the "Synthesis and Biological Effects of Substituted Cyclohexadienes."

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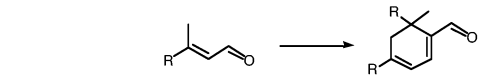
potassium *tert*-butoxide,[9,10] and others.[11] The conditions utilized in these reactions, however, are fairly harsh and illustrate no degree of stereoselectivity.

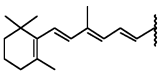
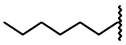
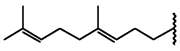
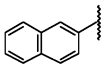
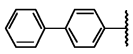
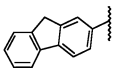
Proline is a widely employed organocatalyst[12] as it is readily available and inexpensive.[13] It has been employed in a variety of asymmetric organic reactions including aldol,[14] Diels−Alder,[15] and Michael addition,[16] among many others.[13] Here, we fully investigate the use of L-proline as a chiral auxiliary to catalyze asymmetric self-condensation of a variety of α,β-unsaturated aldehydes.[17] The scope of the reaction is investigated with 12 different substrates (including a few reported previously for comparison)[17] and 7 proline/proline-based catalysts and the reaction conditions optimized. NMR and MS analyses as well as reactions with various proline derivatives also provide mechanistic insight into the reaction.

Results and Discussion

Initially, we optimized conditions for these reactions (varying the temperature and substrate to catalyst ratios), utilizing citral as a model substrate and L-proline to implement the reaction.

TABLE 1. Effect of Various Substrates on Proline Promoted Homodimerization



[a]R group	Compound	[b]yield	[c]ee (%)
	1a	89	52
	1b	87	62
	1c	47	40
	1d	60	26
	1e	66	40
	1f	73	54
	1g	50	56
	1h	42	51
	1i	65	50
	1j	57	42
	1k	52	36
	1l	62	46

[a] Reaction conditions: 1 equiv of aldehyde and 1.5 equivs of L-proline dissolved in ethanol and stirred at room temperature for 16−24 h. [b] Isolated yield. [c]Determined by $Pr(hfc)_3$ chiral shift reagent

Reactions mediated with other amino acids (Trp, His, Arg, Gly, and Ile) either fail or proceed to a lesser extent than proline.[17] Product yields were highest when the reactions were carried out at room temperature versus −20 to 0 °C or 50−100 °C. Citral dimer **1i** is typically isolated as the sole product in 65% yield following 16−24 h incubation at room temperature (Table 1). This is in contrast to treatment of citral with NaH, which gives a mixture of products **1i** and **1i*** in a 5:95 product ratio (Figure 2).[8b] When the temperature is decreased (−20 to 0 °C), the reaction is sluggish and yields diminish to less than 5%. The majority of the starting material remains as its Schiff base at 48 h. On the contrary, when the temperature is increased, many unidentified byproducts begin to form within 1 h and citral dimer is obtained in less than 10% yield at 16 h. Varying the substrate to auxiliary agent (L-proline) ratios also had a dramatic effect on reaction yields. We evaluated six different substrate-to-catalyst ratios: 1:0.5, 1:1, 1:1.25, 1:1.5, 1:1.75, and 1:2, respectively, whereby 1:1.5 molar concentrations exhibited the highest conversion rates (65%). At 1:0.5, 1:1, and 1:1.25 concentrations, the yields were <5%, 27%, and 42%, respec-

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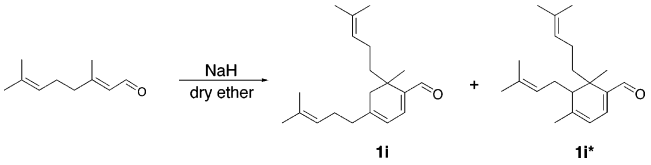


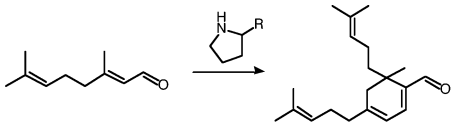
FIGURE 2. Products formed by treatment of citral with NaH.

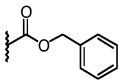
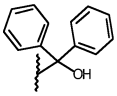
tively. Likewise, at higher proline concentrations, yields were reduced to 37% (1:1.75) and 35% (1:2).

Various substrates were tested utilizing these optimized conditions to investigate the generality of the reaction as illustrated in Table 1. Product yields ranged from 42 to 89% and ee's from 26 to 62%. Treatment of retinal (**1a**, requires added triethylamine)[17] and β-ionylideneacetaldehyde (**1b**) with ethanolic proline gave correspondingly higher yields than those originally reported, and yields are provided for the reaction with senecioaldehyde (**1f**) and citral (**1i**) that were not previously provided.[17] The new substrates examined α,β-unsaturated aldehydes with conjugated chains (**1a** and **1b**), the aromatic aldehydes, thiophene (**1c**) methylfuran (**1d**), and phenyl (**1e**), the aliphatic alkyl substituents (**1g** and **1h**), as well as bulky substituents such as naphthalene (**1j**), biphenyl (**1k**), and fluorene (**1l**). Interestingly, thiophene-substituted (**1c**) gave an unexpectedly lower yield than methylfuran-substituted (**1d**) but gave correspondingly higher ee's. Modest yields were obtained with alkyl substituents (**1g** and **1h**), presumably attributed to the flexibility of the groups versus the more rigid conjugated long chain substituents (**1a** and **1b**) where the highest yields were observed. While we expected the naphthalene (**1j**), biphenyl (**1k**), and fluorene (**1l**) substituents to result in low transformation efficiences due to steric hindrance (attributed to the bulkiness of the side chains), product yields (**1j**, 57%; **1k**, 52%; **1l**, 62%) were remarkably good, comparable to those of others examined. Circular dichroism (CD) analysis of the menthylhydrazone derivatives of the C-30 dimer (formed through dimerization of **1b**) suggests that the absolute configuration of the major isomer formed in these L-proline mediated reactions is the *S*-configuration as determined by the quadrant rule (chiral excition theory).[18]

Since the reaction appeared quite universal, i.e., amenable to a variety of different substrates, we analyzed various proline derivatives to determine their effects on the enantioselectivity of the reaction. Previous work has shown that the reaction can be promoted by *trans*-4-hydroxy-L-proline, D-proline, and *cis*-4-hydroxy-D-proline.[17] Citral (**1i**) was reacted with six different proline derivatives including L-proline methylester (**2a**),[19] isopropyl ester (**2b**),[19] benzyl ester (**2c**),[19] prolinol (**2d**), diethyl prolinol (**2e**),[20] and biphenyl prolinol (**2f**) (see Table 2).[20] To our disappointment, little enantiomeric selectivity (less than 20%) was observed in each case. The highest selectivity was obtained with α,α-diethyl prolinol **2e**, which gave an enantiomeric excess of 15.5%. Reaction yields were moderate with the exceptions of **2c** and **2d**, which generated yields similar to that of L-proline. Solvent effects on citral dimerization were also examined with prolinol (**2d**); THF, DMSO, DMF, and 2-propanol were each examined, but no improvement on

TABLE 2. Effect of Proline Derivatives on Homodimerization



[a]R group	catalyst	time (h)	[b]yield (%)
	2a	5	38
	2b	34	43
	2c	33	72
	2d	23	78
	2e	18	57
	2f	30	49

[a] Reaction conditions: 1 equiv of citral and 1.5 equiv of catalyst dissolved in ethanol and stirred at room temperature for 16−24 h. [b] Isolated yield.

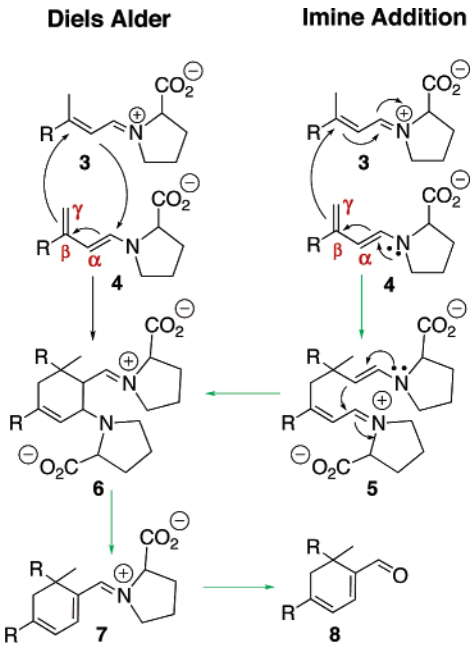


FIGURE 3. Proposed routes to the synthesis of 1,2,4-trisubstituted cyclohexadienals.

enantiomeric selectivity was observed. As with the proline-assisted reaction, ethanol generated the highest yields (78%).

The proline promoted reaction is thought to ensue by nucleophilic attack of the aldehyde with proline, resulting in the formation of a Schiff base **3** (Figure 3). Tautomerization (invoked by deprotonation of the β-methyl group) gives the β-methylenic proline adduct **4** that can be visualized to dimerize

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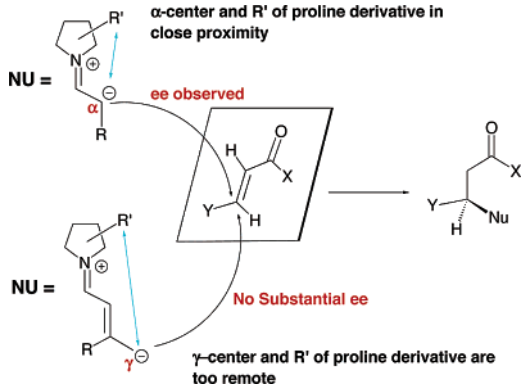

FIGURE 4. Schematic diagram depicting Michael donor and acceptor interactions.

with **3** following a Diels−Alder- or Michael-like imine addition mechanism (pathway marked with green arrows). The need for 1.5 equiv of chiral auxiliary (L-proline) in the reaction is presumably necessary to convert all of the starting aldehyde to that of the Schiff base (accounting for 1 equiv of L-proline), while the additional 0.5 equiv is needed to deprotonate the β-methyl group. In support of this mechanism, many of the proline derivatives listed in Table 2 were capable of catalyzing the reaction in similar yields to that of L-proline. Therefore, proton abstraction is not an intramolecular process involving the proline carboxylate. Additionally, while proline derivatives have been reported to give modest improvements in enantioselectivity over proline itself,[13] in our case no improvement was observed. Hence, the reactive center might be too remote for these derivatized proline chiral auxiliary agents to impart much of an impact. This in turn would suggest that the reaction likely proceeds through imine addition versus a Diels−Alder based mechanism;[8,10,11] the Diels−Alder approach involves the enamine and γ-positions of the diene (Figure 3). On the contrary, the Michael-like imine addition involves only the γ-position, a remote carbon center, of the *cis*-diene. The effect of the chiral auxiliary should be quite pronounced if the reaction followed a Diels−Alder reaction pathway. In further support of this notion, previous reports of proline-assisted Michael additions, where effects on ee's were observed, have involved addition by the α-position of the donor molecule (Figure 4).[16] In our case, we are two carbon atoms removed (addition occurs with the γ-carbon of the donor molecule) and the chiral auxiliary is too far removed to elicit an effect.

To provide additional experimental evidence for our proposed mechanism, we performed a time course analysis of this proline-assisted dimerization reaction by NMR and MS. The results are provided here for the homodimerization of retinal **1a** (Figure 5). Retinal and proline were mixed in an NMR tube. An immediate scan (2 min) revealed formation of the Schiff base (**3**), giving both cis and trans isomers (α-carbon to the protonated imine) at 8.90 and 8.80 ppm, respectively.[21] After 9 min, two new pairs of peaks began to appear corresponding to cis/trans isomers (9.01 and 9.11 ppm, respectively) of intermediate **7**. While full characterization of **7** could not be obtained due to convolution of the spectra, two additional pairs of doublets (7.25 and 7.57 ppm) were detected, corresponding to the coupled cyclohexadiene ring protons. Coupling of the protons was confirmed by H,H-COSY (see Supporting Information). Retinal

(21) Rabiller, C.; Danho, D. *Helv. Chem. Acta* **1984**, *67*, 1254−1273.

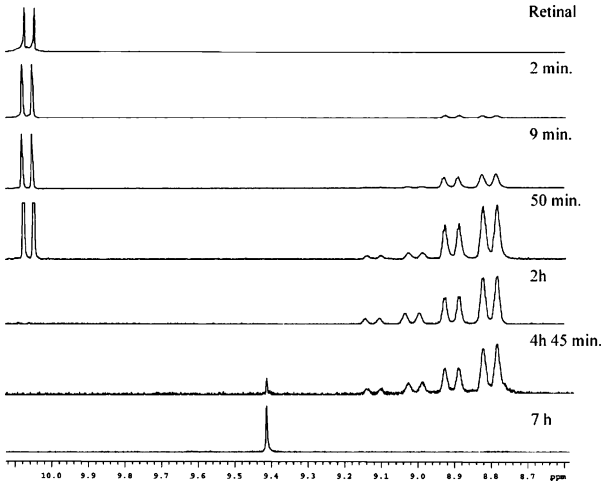

FIGURE 5. Time course analysis of retinal homodimerization by NMR.

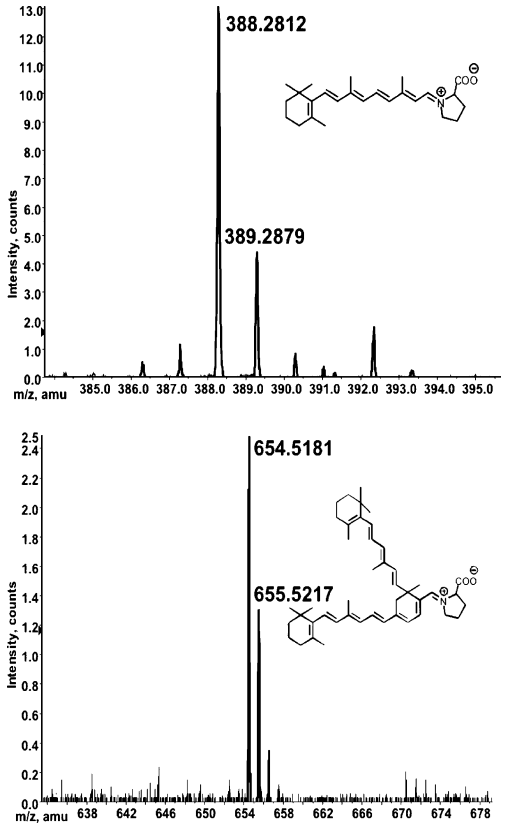

FIGURE 6. Mass spectral peaks (M + Li) observed at 2h 30 min post induction: (top) Schiff base **3** (388.2812 amu) and (bottom) intermediate **7** (654.5181 amu).

was fully consumed by a time of 1 h 20 min postinduction with intermediates **3** and **7** remaining, providing evidence that the condensation reaction occurs between two proline adducts (Figure 3, condensation between **3** and **4**) as opposed to one proline adduct and one aldehyde. At 3 h, triethylamine (1 equiv) was added to facilitate dimer formation.[17] Traces of the C-40 dimer product were apparent by 4 h. The full NMR spectra of these time points are provided as Supporting Information. MS analysis of the reaction was performed at four time points (30 min, 1 h 30 min, 2 h 30 min, and 4 h 30 min). The data were

fully consistent with the NMR results (Figure 6, reaction progression at 2 h 30 min), showing detection of both the Schiff base **3** and intermediate **7**. NMR and MS experiments were also performed with citral (without added triethylamine). The data paralleled those observed with retinal and are included as Supporting Information.

Additionally, we synthesized β-methyl substituted benzylidene aldehyde in deuterated form with the intent of measuring a kinetic isotope effect for the homodimerization reaction. However, a deuterium exchange experiment revealed significant solvent exchange by the reaction. Citral was reacted with proline in deuterated methanol and examined by both MS and NMR . MS analysis revealed the presence of citral dimer labeled with 1 through up to a possible 10 deuteriums. NMR analysis/integration of the peaks confirmed the incorporation of deuterium at the aldehyde position as well as at C-3, C-3′, C-3″, C-5, C-7, and C-1″. The significant exchange observed during the course of this reaction hinders our ability to measure a kinetic isotope effect.

Conclusion

Our results demonstrate the use of proline to promote asymmetric self-condensation of α,β-unsaturated aldehydes to form trisubstituted cyclohexadiene products. Reaction conditions are mild and yet amenable to a variety of different substrates, yielding molecules with complex scaffolds from simple precursors. Mechanistic hypotheses are presented involving condensation between two proline adducts through either a Diels−Alder or Michael-like imine addition. The progress of the reaction was monitored, in time course analyses, by NMR and MS, providing evidence for the intermediacy of Schiff base **3** and protonated imine **7**. Moreover, these experiments revealed the complete loss of starting aldehyde during the reaction in support of a two proline adduct-based mechanism. Additionally, investigations with various proline derivatives gave similar yields to that of L-proline, suggesting that deprotonation and activation of the β-methyl group to give **4** is an intermolecular process and does not involve the proline carboxylate of the Schiff base (**3**). The moderate ee's exhibited by these proline chiral auxiliaries suggest that the reaction likely proceeds through imine addition versus a Diels−Alder-based mechanism since a Diels−Alder would involve two reaction centers, the enamine and γ-positions of the diene (Figure 3), while imine addition would only involve the γ-position, a remote carbon center, of the *cis*-diene.

The approaches presented here will allow diversification and synthesis of these cyclohexadiene ring-fused homodimers in sufficient quantities for biological investigations.

Experimental Section

A. Synthesis of Nitriles. Nitriles **3b**−**e**, **3g**, and **3j**−**l** were synthesized following literature protocols[22] and purified by flash column chromatography (gradient of 2−10% ethyl acetate/hexanes).

3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienenitrile (3b):[23] yield, 94%; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 6.54 (d, 1H, J = 16.2 Hz), 6.11 (d, 1H, J = 16.2 Hz), 5.06 (s, 1H), 2.16 (d, 3H, J = 0.6 Hz), 1.980−2.03 (m, 2H), 1.67 (d, 3H, J = 0.9 Hz), 1.54−1.62 (m, 2H), 1.41−1.46 (m, 2H), 1.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 157.1 (C), 136.1 (C), 135.6 (CH), 132.9 (CH), 130.2 (C) 117.9 (C), 96.6 (CH), 39.6 (CH_2), 34.3, (C), 33.3, (CH_2), 29.0 (2 × CH_3), 21.8 (CH_2), 19.2 (CH_3), 16.5 (CH_3); IR (neat) ν 2925, 2855, 2210, 1738, 1614, 1585, 1455, 1375, 1365, 1217, 966 cm^{-1}. HRMS (ESI) for $C_{15}H_{21}NLi$ $(M + Li)^+$: calcd, 222.1834; found, 222.1828.

B. Synthesis of α,β Unsaturated Aldehydes. α,β-Unsaturated aldehydes were prepared by reduction of their corresponding nitriles (**3b**−**e**, **3g**, and **3j**−**l**) and purified by flash column chromatography (2−10% ethyl acetate/hexanes).[24] Farnesal was synthesized from farnesol.[25] In all cases, the all-trans isomer was utilized in self-condensation reactions.

3-Methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienal (4b):[23] yield: 97%; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 10.09 (d, 1H, J = 8.1 Hz), 6.70 (d, 1H, J = 16.2 Hz), 6.17 (d, 1H, J = 15.9 Hz), 5.89 (d, 1H, J = 7.8 Hz), 2.27 (s, 3H), 2.00 (t, 2H, J = 6.0 Hz), 1.68 (s, 3H), 1.52−1.62 (m, 2H), 1.42−1.45 (m, 2H), 1.00 (s, 6H);^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 191.1 (CH), 157.2, (C), 136.1 (C), 135.6 (CH), 132.8 (CH), 132.5 (C), 130.2 (CH), 39.6 (CH_2), 34.2 (C), 33.2 (CH_2) 28.9 (2 × CH_3), 21.7 (CH_2), 19.1 (CH_3), 16.5 (CH_3); IR (neat) ν 2930, 2865, 1738, 1665, 1606, 1448, 1376, 1364, 1216, 1206, 1116, 963, 764, 749, 732 cm^{-1}. HRMS (ESI) for $C_{15}H_{22}OLi$ $(M + Li)^+$: calcd, 225.1831; found, 225.1835.

Synthesis of Self-Condensation Products. Ring-fused homodimers were generated by self-condensation of α,β-unsaturated aldehydes, a modification of Asato et al.[17] The generalized approach is illustrated below for 6-methyl-4,6-di-thiophen-2-yl-cyclohexa-1,3-dienecarbaldehyde (**1c**).

6-Methyl-4,6-di-thiophen-2-yl-cyclohexa-1,3-dienecarbaldehyde (1c). To an oven-dried flask was added 3-thiophen-2yl-but-2-enal (**3c**) (20 mg, 0.132 mmol) dissolved in 10 mL of 200 proof ethanol. To this solution was added L-proline (23 mg, 0.200 mmol). The mixture was allowed to stir at rt for 24 h prior to quenching the reaction with deionized H_2O (30 mL) and extraction with hexanes (3 × 50 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (5% ethyl acetate/hexanes) afforded 17.7 mg of **1c** as a red oil (47%): ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 9.49 (s, 1H), 7.35−7.40 (m, 1H), 7.28−7.30 (m, 2H), 7.05−7.14 (m, 3H), 6.93 (d, 1H, J = 6.0 Hz), 6.62 (dd, 1H, J = 0.9, 6.3 Hz), 3.21 (d, 1H, J = 17.4 Hz), 2.93 (dd, 1H, J = 1.5, 17.4 Hz), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 192.0 (CH), 152.4 (C), 143.7 (CH), 142.2 (C), 141.5 (C), 138.8 (C), 128.6 (CH), 128.6 (CH), 128.5(CH), 127.9 (CH), 126.6 (CH), 126.2 (CH), 123.6 (CH), 45.2 (CH_2), 29.9 (C), 27.2 (CH_3); IR (neat) ν 3006, 2928, 2855, 1738, 1455, 1365, 1217, 764 cm^{-1}. HRMS (ESI) for $C_{16}H_{14}OS_2Li$ $(M+Li)^+$: calcd, 293.0646; found, 293.0654.

C. Determination of Absolute Configuration. CD analysis of the menthylhydrazone derivatives of C-30 dimer **1c** suggests that the major isomer in these instances is in the *S*-configuration as determined by the quadrant rule (chiral excitation theory).[18]

D. Preparation of Retinal Samples for NMR Analysis. A 30 mg/mL solution of all-trans retinal, L-proline, and triethylamine was prepared by dissolving each in CD_3OD. These were stored at −20 °C until further use.

E. NMR Analysis of Retinal Self-Condensation Reaction. A 5 mm NMR tube was filled with 800 μL of CD_3OD and then placed in a 300 MHz NMR spectrometer. Once properly shimmed, another tube was filled with 500 μL of all-*trans*-retinal (30 mg/mL, 0.05278 mmol) and the instrument reshimmed. The reaction was started by ejecting the all-*trans*-retinal and adding 304 μL, 1.5 equiv, of the L-proline solution (30 mg/mL, 0.07921 mmol), shaking the tube,

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reinserting the tube into the NMR, and immediately acquiring a spectrum that took a total time of 2 min. After the initial spectrum the instrument was periodically reshimmed. After 3 h 30 min, all of the all-*trans*-retinal had been consumed and all that existed was Schiff base **3** and intermediate **7** at which time the NMR tube was removed and 180 μL of triethylamine (30 mg/mL, 0.5340 mmol) was added followed by shaking and reinsertion of the tube. After a few minutes, formation of the C-40 retinal dimer was present. After 2 h 30 min, the reaction was complete. Spectra were acquired over an 8-h period at various time points.

MS analysis of the reaction was taken at 30, 90, 150, and 270 min. Intermediates **3** (M + Li = 388.2812 amu) and **7** (M + 654.5181 amu) were both observed.

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Supporting Information Available: Experimental procedures, additional characterization data, ^{1}H and ^{13}C NMR spectra, and details on isotopic labeling studies are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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