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Stereochemically Probing the photo-Favorskii Rearrangement: A Mechanistic Investigation

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Abstract

Using model (*R*)-2-acetyl-2-phenyl acetate esters of (*S*)- or (*R*)- α -substituted-*p*-hydroxybutyrophenones (*S,R*)-**12a** and (*R,R*)-**12b**, we have shown that a highly efficient photo-Favorskii rearrangement proceeds through a series of intermediates to form racemic rearrangement products. The stereogenic methine on the photoproduct, *rac*-2-(*p*-hydroxyphenyl)propanoic acid (*rac*)-**9**, is formed by closure of a phenoxy-allyloxy intermediate **17** collapsing to a cyclopropanone, the “Favorskii” intermediate **18**. These results quantify the intermediacy of a racemized triplet biradical ³**16** on the major rearrangement pathway elusively to the intermediate **18**. Thus, intersystem crossing from the triplet biradical surface to the ground state generates a planar zwitterion prior to formation of a Favorskii cyclopropanone that retains no memory of its stereochemical origin. These results parallel the mechanism of Dewar and Bordwell for the ground state formation of cyclopropanone **3** that proceed through an oxyallyl zwitterionic intermediate. The results are not consistent with the stereospecific S_N2 ground state Favorskii mechanism observed by Stork, House, and Bernetti. Interconversion of the diastereomeric starting esters of (*S,R*)-**12a** and (*R,R*)-**12b** during photolysis did not occur thus ruling out leaving group return prior to rearrangement.

Keywords

Photochemistry; Stereochemistry; Photo-Favorskii rearrangement; triplet biradical; *p*-Hydroxyphenacyl; Zimmerman paradigm

Introduction

The *p*-hydroxyphenacyl (PHP) chromophore has been established as a clean, efficient photoremovable protecting group (PPG) for nucleofuges such as phosphates, sulfonates, carboxylates, and certain thiols and phenols.^{1,2} The chromophore imparts good hydrophilicity, excellent biological compatibility, and relatively easy installation of the protected moiety. In aqueous media, the photorelease is accompanied by rearrangement of the chromophore, originally described as a photo-Favorskii rearrangement by Reese and Anderson,³ that results in a dramatic hypsochromic shift in its absorption spectrum. The release of the leaving groups occurs rapidly ($k_r = 10^8$ – 10^9 s⁻¹) in quantitative chemical yield and the quantum yields approach 1.0. Together, these properties have encouraged us and

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This article is dedicated to the memory of Professor Howard E. Zimmerman, University of Wisconsin, Madison (July 5, 1926 – February 11, 2012).

Supporting Information Available: ¹H, ¹³C NMR, absorption and HRMS spectra are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

others to investigate further applications² including the new chemical transformations such as ring contraction reactions.⁴ In turn, there has been a renewed interest in the mechanism of the photo-Favorskii rearrangement, itself.^{1,5,6}

For example, controversy surrounds the extent to which two transient intermediates, the triplet biradical **32** and the spirodienone **3**, play a role in the photo-Favorskii rearrangement. The chronological sequence which we embraced for the photo-Favorskii rearrangement (Scheme 1) includes **32** and **5**, two detectable transients using time-resolved (TR) transient absorption spectroscopy.^{5b} The earliest transient (λ_{max} 445 and 455 nm) has been assigned the structure of the triplet allyloxy-phenoxy biradical (**32**), which is formed from **31**. It decays with a rate constant of $k_{\text{birad}} = 1.5 \times 10^9 \text{ s}^{-1}$ to form cyclopropanone **3**, the “Favorskii” intermediate,³ which has eluded detection thus far. Nevertheless, **3** serves as the necessary bridge between the structure of the pHP chromophore in **1** and its photoproducts, *p*-hydroxyphenylacetic acid (**4**) and *p*-hydroxybenzyl alcohol (**6**). Phenylacetic acid **4** is formed from hydrolysis of **3** whereas decarbonylation forms **5** (a *p*-methylenequinone) that hydrolyzes to *p*-hydroxybenzyl alcohol **6**.^{5b,7} However, evidence for intermediate **2** and its subsequent conversion to **3** is incomplete and circumstantial, leading others to propose alternative mechanisms that either bypassed the biradical **32** intermediate^{5c,6a–g} and, in at least one report,^{6h} completely disregarded the Favorskii cyclopropanone **3**, altogether.

The stereochemical integrity of the migrating methylene group should serve as a quantitative measure by the degree of racemization resulting from formation of a racemic intermediate such as biradical **2**. Indeed, stereochemistry has often been employed in mechanistic investigations for both ground state and photochemical rearrangements as documented, for example, in the earlier work of Zimmerman’s studies of the Type A photorearrangements of dienones.⁸ Relevant examples are studies of the stereochemistry of the ground state Favorskii rearrangement extensively examined by House,⁹ Sorenson,¹⁰ Bernetti,¹¹ and by Bordwell.¹² The seminal studies by Loftfield¹³ on the 1,2-carbon migration later challenged by Dewar’s theoretical treatment¹⁴ now serve as the two limiting mechanisms for the base-promoted Favorskii rearrangement. Loftfield’s one-step concerted S_N2 process contrasts with Dewar’s two-step preformation of an oxyallyl zwitterion intermediate prior to cyclization by disrotatory closure¹⁵ to generate the Favorskii cyclopropanone intermediate. While both mechanisms involve the intermediacy of a cyclopropanone, the stereochemical consequences of a migrating stereogenic carbon are clearly distinguishable and both limiting mechanisms have experimental support.^{8–11,16,17,18}

With this abundance of precedent of the limiting ground state mechanisms, we were persuaded to pursue the stereochemistry of the photochemically driven Favorskii rearrangement. Our model employs a *p*-hydroxybutyrophenone equipped with a chiral leaving group thus providing us with a pair of diastereomeric esters to test the stereochemical changes at the migrating carbon.

Results and Discussion

A convenient framework for testing the two limiting Favorskii rearrangement pathways is depicted in Scheme 2 using *p*-hydroxybutyrophenone **7**. The stereochemical integrity of the migrating α -carbon (marked as *) was monitored by HPLC (chiral stationary phase) and by ¹H NMR.

Extension of the pHP aliphatic chain to *p*-hydroxybutyrophenone raises the possibility of photochemical competition by a Norrish Type II fragmentation instead of the photo-Favorskii rearrangement.¹⁹ However, when the normally efficient Type II reaction was pitted against the photo-Favorskii rearrangement with a series of *o*-methyl pHP analogs, the

Type II reaction could be completely quenched by photolysis in solutions containing >15% H₂O which gave *exclusively* photo-Favorskii products. Solvents with less than 10% H₂O yielded only Type II products.²⁰

Synthesis and assignment of stereochemistry

Enantiomerically pure (*R*)-2-acetoxyphenylacetic acid (*R*)-**11** was reacted with α -bromo-*p*-hydroxybutyrophenone (*rac*-**10**) through an S_N2 displacement of bromide to provide the pair of diastereomeric esters **12a,b** as a 1:1 mixture (Scheme 3).^{21,22}

Choice of the leaving group **11** served the dual purpose of creating a pair of separable diastereomeric esters as well as a direct, internal diagnostic for assigning the configuration of the butyrophenone stereogenic center. The assignment of the absolute configuration of each diastereomer²³ was based on the shielding effects of the (*R*)-**11** aryl ring on identifiable elements on the butyrophenone fragment. Using chemical shift correlations analogous to those described by Trost for an *O*-methylmandelate model²⁴ (Figure 1), the configurations of (*S*)-1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate for **12a** and (*R*)-1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate for **12b** were assigned.

Photochemistry

The 1:1 diastereomer mixture of **12a,b** (30 mmol in 0.6 ml of 4:1 CD₃CN:D₂O) was irradiated in an NMR tube for 49 min. to nearly complete conversion using a Rayonet reactor equipped with two 15 W 300-nm lamps. Two major products were detected by ¹H NMR analysis of the crude reaction mixture; the chiral leaving group (*R*)-**11** (100%) and the rearranged 2-(4-hydroxyphenyl)butanoic acid²⁵ (**9**, 82%). Two minor products, 4-(1-hydroxypropyl)phenol (**13**, 7%)²⁶ and 2-hydroxy-1-(4-hydroxyphenyl)butan-1-one (**14**, 3%) were also detected and identified (Fig. 2 and Figure 7, Experimental Section). Hydroxy acid **14** is apparently formed by photohydrolysis whereas the benzyl alcohol **13**, a ubiquitous minor product in our studies, is formed from the photo-Favorskii cyclopropanone **18**. Decarbonylation of **18** gave 4-propoylidencyclohexa-2,5-dien-1-one (**19**), an analog of *p*-methylenequinone (**5**, Scheme 2), which hydrolyzes to **13**. No evidence for competing Type II photoreaction of the butyrophenone was observed as anticipated when H₂O solvents are employed.^{19,20}

The stereochemical consequences of the rearrangement were assessed by irradiation of the individual diastereomers. Photolysis of (*S,R*)-**12a** produced racemic α -arylbutanoic acid (*rac*-**9**; See Supporting Information). Complete racemization was confirmed for the reaction when diastereomeric (*R,R*)-**12b** also gave only racemic products (Scheme 5).

In a control reaction monitored by ¹H NMR, **12a** was not converted to its diastereomer **12b** during photolysis ruling out a recombination reaction which would generate the diastereomeric mixture of the esters (Fig. 3), thus assuring the integrity of starting esters (*S,R*)-**12a** and (*R,R*)-**12b** throughout the photolysis and demonstrating that *rac*-**9** was not the result of an *a priori* equilibration of the stereogenic center (Scheme 5). Quantum yields are also consistent with irreversible release of the acid ($\Phi_{\text{dis}} = 0.54 (\pm 0.05)$ for **12a** and **b**) and are among the most efficient pHP arboxylates.

A remaining fundamental questions are the nature of the ring closure to cyclopropanone **3** which is not defined in Scheme 1 and the origin of the hydroxyketone **14** which does not appear in most treatments of the photo-Favorskii reaction mechanism. Here we draw upon the Zimmerman paradigm developed in his early work on the photorearrangement of 2,5-cyclohexadien-1-one to bicycle[3.1.0]hexenone. He suggested that photochemical reactions

might be viewed as four common steps: (1) excitation, (2) adiabatic bond alteration and (3) demotion or relaxation to the ground state energy surface where (4) further bond alteration is proceeding along a classical ground state surface to the final photoproducts.^{8,27} Steps 2 and 4 are classical electron pushing approaches toward defining a mechanism. We have applied the approach to the photorearrangement of **12a,b** and to our recent study on photo-Favorskii ring contraction reaction of cyclic analog **20** shown together in Scheme 6.

Formation of cyclopropanone **18** (or **24**) is a prohibitively high energy process on the triplet excited state surface^{5b} and is spin forbidden; therefore, it must occur from a relaxed singlet oxyallyl biradical (open shell) or closed shell counterpart, the ground state Dewar zwitterion (Scheme 2). In ground state Favorskii rearrangements where the Dewar mechanism obtains, the reaction leads to complete loss of the stereochemical integrity of the α -carbon. For our photo-Favorskii study, the α -carbon is completely racemized at the final product stage, e.g. *rac*-**9**, thus quantifying the extent of involvement of the oxyallyl biradical **16** intermediate. In our previous study, the transient nature of the oxyallyl biradical limited our assessment of its relative significance as an intermediate in the formation of the phenylacetic acid.^{5b}

The two minor products from the photo-Favorskii rearrangement, hydroxyphenol **13** and hydroxyketone **14** provide additional insight. The hydroxyphenol **13**, always seen as a minor product, is formed by decarbonylation of the cyclopropanone **18** followed by hydrolysis^{4,5b,6} yielding racemic *p*-hydroxyphenyl propanol ((\pm)-**13**; Scheme 6). We previously denoted this product as a signature of the intermediacy of the Favorskii cyclopropanone **18**.^{5,6}

The origin of the hydroxyketone **14** is less apparent and less frequently encountered. Corri and Wan^{5c} first reported this minor photohydrolysis product which we have subsequently confirmed.^{4,5a,b,d} Most recent, cycloalkanone **20** (Scheme 6), which may be viewed as having the terminal carbon of the butyl group on butyrophenone bonded directly to the aryl ring, yields a hydroxyketone, e.g. **23**, as the major photoproduct (57% vs. 3% for **14**) upon photolysis.⁴ In solvent containing ¹⁸O-labeled water, the hydroxyl group was contained the ¹⁸O-label. The mechanism that incorporates the previous findings with this stereochemical study suggests that the hydrolysis reaction also results from divergence of the closure pathway for the zwitterion **21** toward reaction with the solvent. The very minor proportion of the bifurcation from Favorskii toward hydrolysis this reaction is the lack of steric or strain interfering with ring closure for **17** *vis-a-vis* **22**. The previous study demonstrated that ring strain was a major factor in the partitioning of the two pathways: smaller cycloalkanone rings favored formation of the hydroxyketone while larger rings and acyclic ketones gave predominantly the rearranged acids.⁴ The low yield of **14** from **12** accords well with the increase in ring strain of **24**. The results further suggest that the butyryl group does not cause sufficient steric congestion to divert zwitterion **17** away from the Favorskii pathway. It is noteworthy that the quantum efficiencies are not diminished, supporting the conclusion that the changes in product ratios are independent of the photorelease of the leaving group, but are subject to the partitioning of a common intermediates, e.g. the zwitterions **17** and **22**. Similar results are found for the ground state, ZnCl₂-catalyzed Favorskii rearrangements of the corresponding bromides where the formation of the same two products are formed by competition between solvolysis and rearrangement.^{4,28} These results support a mechanism where the rearrangements emanate from a ground state zwitterion **17**, i.e., step 4 in the Zimmerman paradigm.^{8,27}

Conclusions

The most attractive sequence that accomplishes both the rearrangement and complete equilibration of the stereogenic center to form *rac*-**9** begins with the irreversible heterolysis

of the leaving group from the chromophore from the chiral triplet, $^3\mathbf{12a}$ or $^3\mathbf{12b}$, forming an achiral, and planar triplet biradical $^3\mathbf{16}$. All subsequent products must be racemic. Subsequent relaxation of the triplet biradical $^3\mathbf{16}$ to its open shell singlet $^1\mathbf{16}$ then to the closed shell Dewar intermediate $\mathbf{17}^{29}$ followed by ring closure of the oxyallyl-phenoxy intermediate provides a route to the racemic products (Scheme 6). Furthermore, the triplet biradical $^3\mathbf{2}$ observed in our earlier TR laser flash absorption studies^{5b} accounts for the complete racemization.

The results do not accord with a stereospecific, S_N2 -like pathways analogous to those observed for several ground state Favorskii rearrangements, *e.g.*, the work of Stork,^{16a} House,⁹ Bernetti,¹¹ and Sorenson.¹⁰ Instead, the complete racemization of PHP analogs involves an oxyallyl-phenoxy intermediate paralleling the ground state mechanism of Dewar¹⁴ and documented by Bordwell.^{12,17} Alternative routes, *e.g.*, equilibration of the starting esters or a concerted formation of *p*-hydroxybenzyl acylium intermediates,^{6h} do not occur.

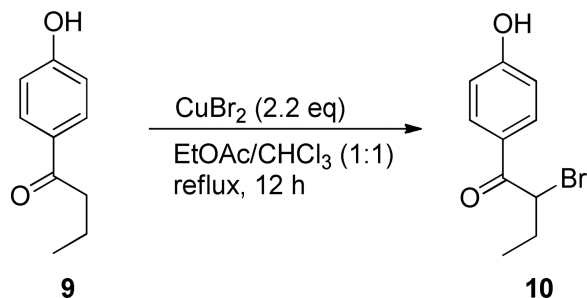
Experimental

General Information

NMR spectra were recorded on a 400 MHz instrument, equipped with a quadruple-band gradient probe (H/C/P/F QNP) or a 500 MHz with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were recorded with broad-band decoupling. Chiral HPLC was performed using Chiralcel OD-H column (250 \times 4.6 mm, 10% IPA in hexanes) using a UV-VIS detector tuned to 254 nm. Photolysis studies were carried out in a rotating merry-go-round apparatus fitted into a Rayonet reactor equipped with two 15 W 300-nm lamps.

Anhydrous acetonitrile was obtained by passing degassed HPLC-grade consecutively through two columns filled with activated alumina. Anhydrous DMF was obtained by distillation of ACS-grade DMF over calcium hydride under a nitrogen atmosphere. α -Bromo-*p*-hydroxybutyrophenone $\mathbf{10}$,³⁰ 4-(1-hydroxypropyl) phenol ($\mathbf{13}$)²⁶, and racemic 2-(4-hydroxyphenyl)butanoic acid ($\mathbf{9}$)²⁵ have been described previously. (*R*)-(-)-*O*-Acetylmandelic acid ((*R*)- $\mathbf{11}$) is commercially available.

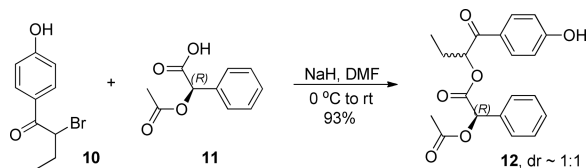
Synthesis of α -bromo-*p*-hydroxybutyrophenone ($\mathbf{10}$)



A 50 mL RBF was charged with 1.00 g (6.09 mmol) of 1-(4-hydroxyphenyl)butan-1-one, 2.99 g of CuBr_2 (13.4 mmol) and 30 mL of 1:1 EtOAc/ CHCl_3 . The heterogeneous solution was brought to reflux and, with vigorous stirring, preceded for 12 h. After this time, the solution was cooled to room temperature, and supervening filtration through a plug of silica afforded, after inspissation, 1.50 g of a white, crystalline material that, through ^1H NMR analysis (CDCl_3) adduced 2-bromo-1-(4-hydroxyphenyl)butan-1-one (**9**) as the primary product with trace amounts of the starting material and the dibrominated analog. Isolation of

10 was not essential for the next reaction step; however, could be achieved by flash chromatography with EtOAc/Hex (1:2) as the eluent.

Synthesis of 1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate (**12a,b**)



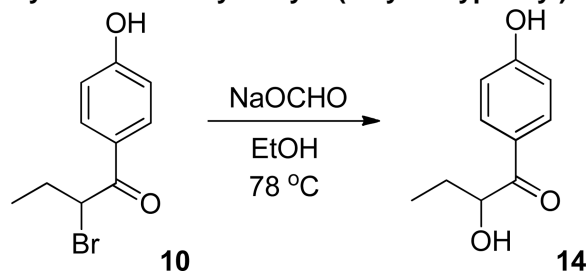
A flame-dried 50 ml RBF was charged with 1.00 g (5.15 mmol) of (*R*)-2-acetoxy-2-phenylacetic acid **11** and 20 ml of dry DMF. The corresponding solution was cooled to -10 °C with an ice/saturated, aqueous NaCl bath, when, while vigorously stirring, 206 mg of NaH (60% w/w in mineral oil, 5.15 mmol) was added. The suspension brought to room temperature with further stirring for 30 minutes before 1.04 g (4.29 mmol) of **9** (2-bromo-1-(4-hydroxyphenyl)butan-1-one, racemic) was added. The reaction proceeded overnight, after which the solution was diluted with EtOAc and washed profusely with H₂O. Flash column chromatography (1:1 EtOAc/Hex) afforded 1.71 g of **12a** ((*R*)-1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate (*R*)-pHP (*R*)-APAc)) and **12b** ((*S*)-1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate (*S*)-pHP (*R*)-APAc)) as a ~1:1 mixture, in 93% yield, as white crystalline solid.

Resolution of the diastereomeric mixture was accomplished as follows: a 1:1 mixture of diastereomers **12a,b** was dissolved in minimum amount of hot ether and dichloromethane (~3:1), and refluxed until all solid was dissolved. Cyclohexane was added gradually, until crystals began to form. The mixture was then cooled in a refrigerator overnight. Crystals were collected by vacuum filtration to give (*R,R*)-**12b** with 90% dr. Mother liquor was concentrated to give (*S,R*)-**12a** with 85% dr. Additional recrystallization of the diastereomers from ethyl acetate provided (*R,R*)-**12b** and (*S,R*)-**12a** with >98% dr as determined by ¹H NMR analysis. The absolute configurations of the resolved esters were established by ¹H NMR using chemical shift correlations analogous to the Trost's model developed for *O*-methylmandelates (Figure).²⁴ The extended Newman projections **A** and **B** with omitted intervening ester linkage represent the most stable conformations, which contribute the most to the observed chemical shifts of diastereomers (*S,R*)-**12a** and (*R,R*)-**12b**. The substituents shown in blue, eclipsing the mandelate phenyl rings (shown in red) are expected to be shifted upfield as a result of anisotropic shielding interaction. Accordingly, the absolute configuration (*S,R*) was assigned to diastereomer **12a** based on the observed upfield shift of a triplet component of the A₃X₂ system corresponding to the ethyl group (0.75 ppm). Analogously, shielding of both doublet components (6.79 and 7.78 ppm) of the AA'XX' system corresponding to the *para*-substituted aromatic ring allowed for assigning the (*R,R*)-configuration to diastereomer **12b** (Figure).

(*S,R*)-**12a**: m.p. 154–155 °C. ¹H NMR (500.13 MHz, CD₃CN) δ 7.94–7.76 (m, 2H), 7.56 (dd, *J* = 6.6 Hz, 2.8 Hz, 2H), 7.49–7.43 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.02 (s, 1H), 5.76 (dd, *J* = 8.7 Hz, 3.9 Hz, 1H), 2.15 (s, 3H), 1.93–1.83 (m, 1H), 1.86–1.71 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125.76 MHz, CD₃CN) δ 195.1, 171.4, 169.8, 163.3, 135.4, 132.3 (2C), 130.7, 130.1 (2C), 129.2 (2C), 127.9, 116.8 (2C), 78.6, 75.7, 26.1, 21.2, 10.3; FT-IR (KBr, cm⁻¹): 3202, 2980, 1757, 1742, 1726, 1686, 1659, 1603, 1570, 1518, 1458, 1441, 1373, 1267, 1227, 1215, 1173, 1097, 1055, 1041, 933, 901, 856, 843, 750, 698, 685, 623, 513; HRMS (TOF ESI) calculated for M+Li = C₂₀H₂₀O₆Li: 363.1420; Found: 363.1423.

(*R,R*)-12b: m.p. 166–167 °C. ^1H NMR (500.13 MHz, CD_3CN) δ 7.76 (d, J = 8.8 Hz, 2H), 7.79 (br. s., 1H), 7.49 (dd, J = 6.5 Hz, 3.0 Hz, 2H), 7.45–7.40 (m, 3H), 6.82 (d, J = 8.8 Hz, 2H), 6.01 (s, 1H), 5.80 (dd, J = 8.0 Hz, 4.3 Hz, 1H), 2.11 (s, 3H), 1.98–1.88 (m, 1H), 1.82–1.72 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3CN) δ 194.7, 171.2, 169.4, 162.9, 134.7, 131.9 (2C), 130.3, 129.7 (2C), 129.0 (2C), 127.6, 116.4 (2C), 78.3, 75.2, 25.7, 20.9, 9.9; FT-IR (KBr, cm^{-1}): 3364, 2984, 1747, 1730, 1688, 1599, 1585, 1512, 1441, 1375, 1350, 1281, 1265, 1231, 1213, 1173, 1097, 1057, 935, 901, 856, 843, 750, 696, 685, 669, 660, 615, 532, 513, 401. HRMS (TOF ESI) calculated for $\text{M}+\text{H} = \text{C}_{20}\text{H}_{21}\text{O}_6$: 357.1338; Found: 357.1339.

Synthesis of 2-hydroxy-1-(4-hydroxyphenyl)butan-1-one (**14**)—



2-Hydroxy-1-(4-hydroxyphenyl)butan-1-one was obtained from bromide **10** following the previously reported procedure.^{6d} Sodium formate (3.82 g, 112.2 mmol) was dissolved in ethanol (150 mL) and bromide **10** (2.124 g, 8.74 mmol) was added. The resulting mixture was stirred at reflux (78 °C) for 1 day, after which time the mixture was filtered hot and concentrated in vacuo. The crude residue was crystallized from ethyl acetate:hexane to give 2-Hydroxy-1-(4-hydroxyphenyl)butan-1-one (**14**) (0.757 g, 4.2 mmol, 48%) as white crystalline solid. m.p. 123–124 °C. ^1H NMR (500.13 MHz, CD_3CN) δ 7.89 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 4.99 (br. s., 1H), 3.69 (d, J = 6.3 Hz, 1H), 2.34 (br. s., 1H), 1.87 (dtd, J = 14.4 Hz, 7.3 Hz, 3.9 Hz, 1H), 1.55 (dq, J = 14.3 Hz, 7.2 Hz, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125.76 MHz, CD_3CN) δ 201.4, 163.0, 132.2 (2C), 127.3, 116.4 (2C), 74.4, 29.8, 9.4; FT-IR (KBr, cm^{-1}): 3223, 3072, 3026, 2968, 2935, 2912, 2876, 1663, 1603, 1591, 1516, 1445, 1439, 1406, 1313, 1279, 1256, 1238, 1167, 1128, 1113, 1092, 1059, 970, 960, 874, 852, 841, 829, 810, 771, 735, 712, 677, 613, 509, 494; HRMS (TOF ESI) calculated for $\text{M}^+ = \text{C}_{10}\text{H}_{12}\text{O}_3$: 180.0786; Found: 180.0786.

General procedure for photolysis: Ester **12a** (11 mg, 0.03 mmol) was placed in an NMR tube and dissolved in a 4:1 mixture of $\text{CD}_3\text{CN}:\text{D}_2\text{O}$. The sample was irradiated in a Rayonet reactor equipped with two 15 W RPR3000 lamps for 50 min. The reaction course was monitored by ^1H NMR (Figure). The NMR yield of the released (*R*)-2-acetoxy-2-phenylacetic acid (**11**) and the rearranged product **9** was found to be 100% and 82%, respectively. Upon completion of the reaction, the crude mixture was concentrated and the main products were isolated by acid-base extraction. The products identity was confirmed by comparison of their ^1H and ^{13}C NMR spectra with those of the authentic samples. The identities of the minor side products were established by spiking the reaction mixture with authentic samples of the corresponding compounds (Figure 6).

Quantum yield measurements

Actinometry: Light output (in mEinsteins/min) was measured by the potassium ferrioxalate method.³¹ The solutions were prepared and irradiated as described above in the General Procedure. The ^1H NMR spectra of the sample were measured at 10 min intervals for up to 40 min. Proton signal of the remaining starting material (singlet at 6.0 ppm) was integrated

against signals of DMF as the internal standard. The results are given in the **Results and Discussion** section.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. See the Experimental section for more detail on the synthesis and stereochemical assignments and Supporting Information for spectra and details on the photo racemization results.
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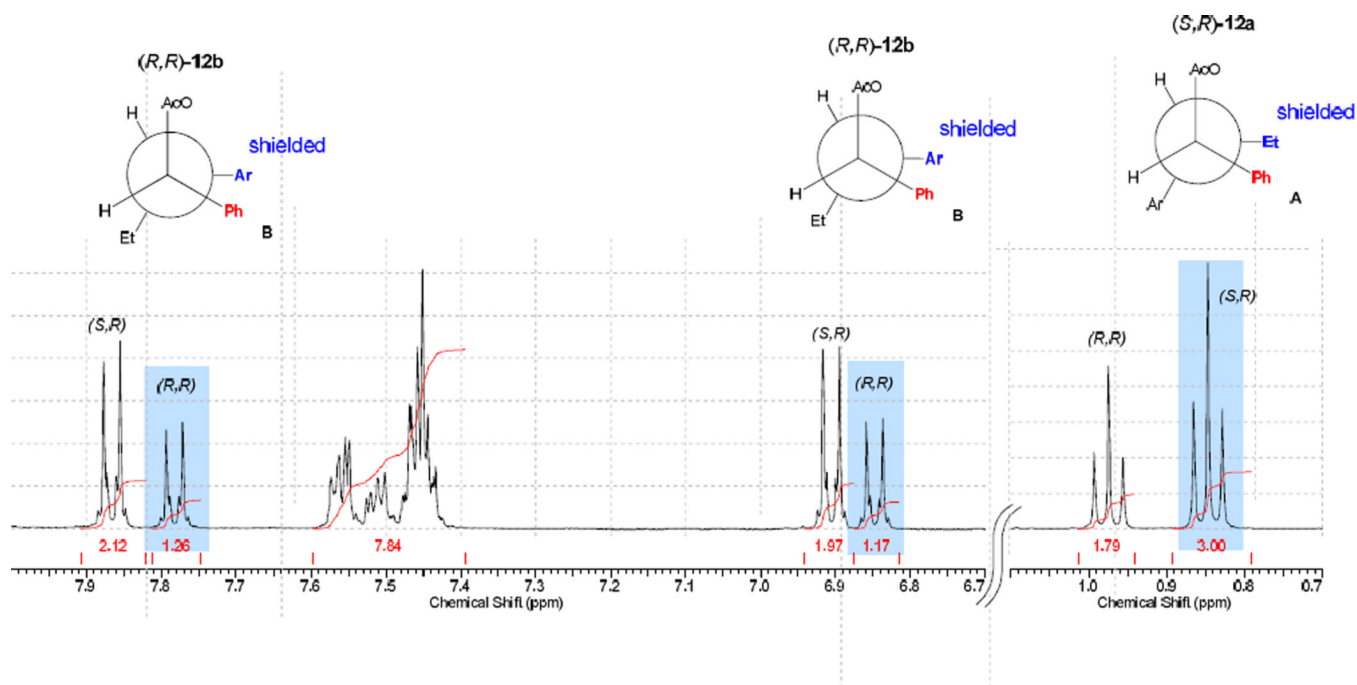


Figure 1.

Fragments of ^1H NMR chart of a diastereomeric mixture **12a** and **12b**. The intervening carboxyl groups on structures A and B are omitted in order to emphasize the phenyl-aryl and phenyl-ethyl shielding interactions for the most stable rotamers of (S,R) -**12a** and (R,R) -**12b**, the major contributors to the shielding effects for the chemical shift differences. The more shielded component (highlighted in blue) of each diastereomer is shown to be eclipsed by the phenyl ring of **11** (shown in red).

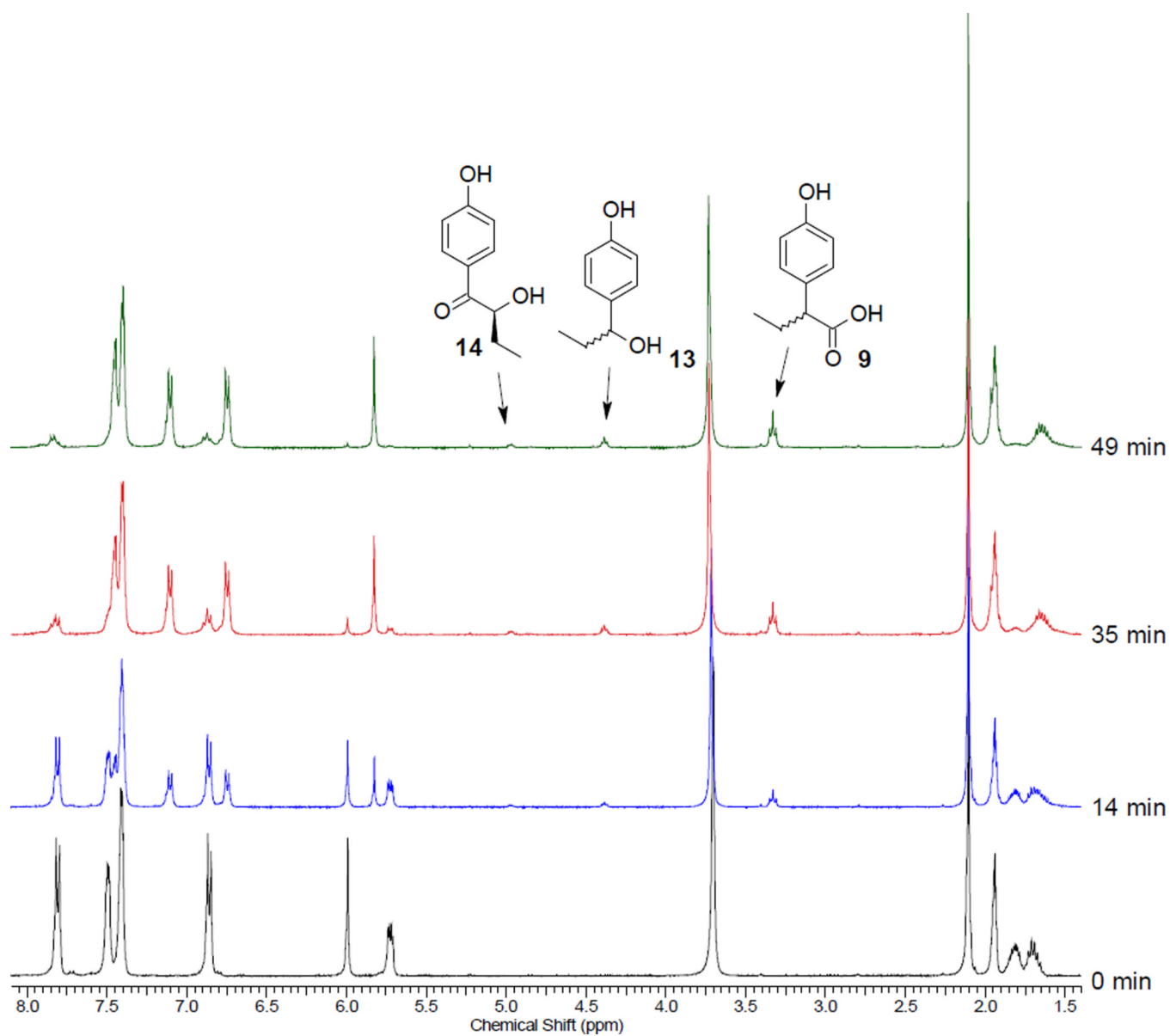


Figure 2. ^1H NMR spectra during photolysis of **12a**. The arrows point to the stereogenic methine protons for the two minor (**13** and **14**) and the major (**9**) products. See Figure 6 (Experimental section) for the assignments.

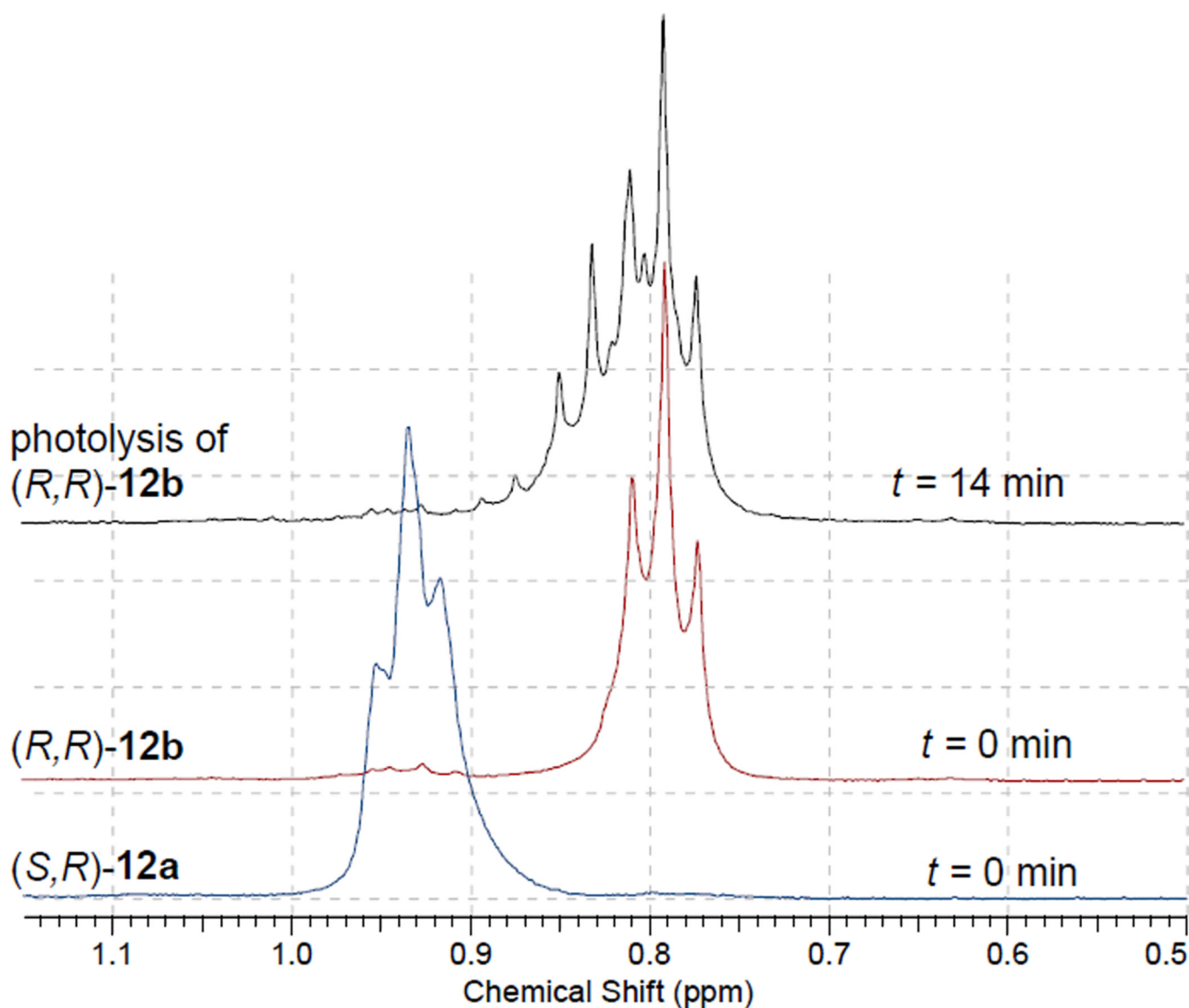


Figure 3. Portions of ¹H NMR spectra of **12b** at $t = 14$ min (top) at 40% conversion at $t = 0$ min for **12b**, and at $t = 0$ min. (lower) for **12a**. The broadening and added complexity of the ¹H NMR signals at $t = 14$ min surrounding the terminal CH₃ group at 0.8 ppm arise from the contributions from the terminal CH₃ groups of products **9**, **13**, and **14**. (See **Experimental** for further details.)

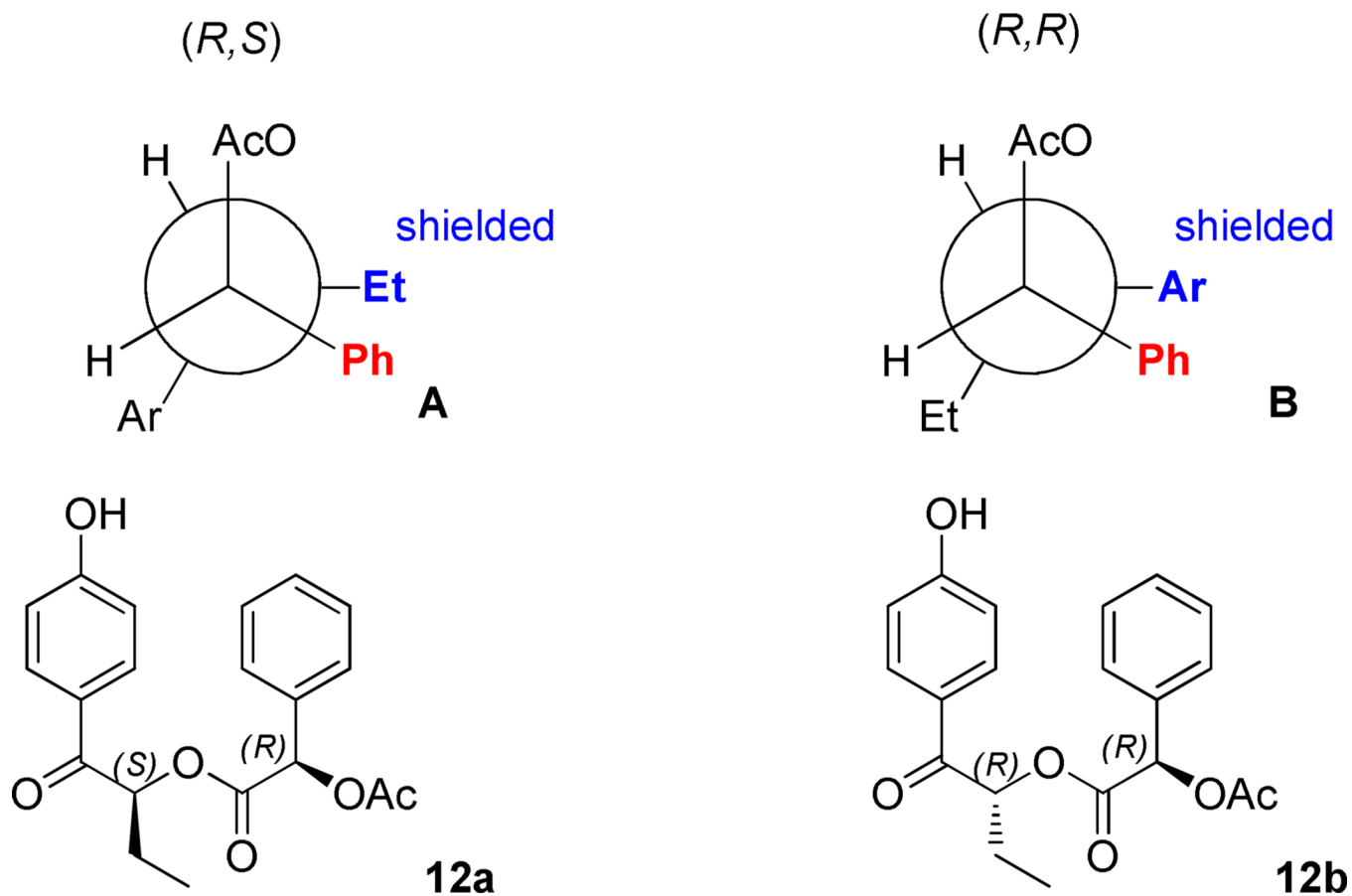


Figure 4.
Chemical shift correlation model for assigning the absolute configurations of (*S,R*)-pHP
(*R*)-APAc **12a, b**.

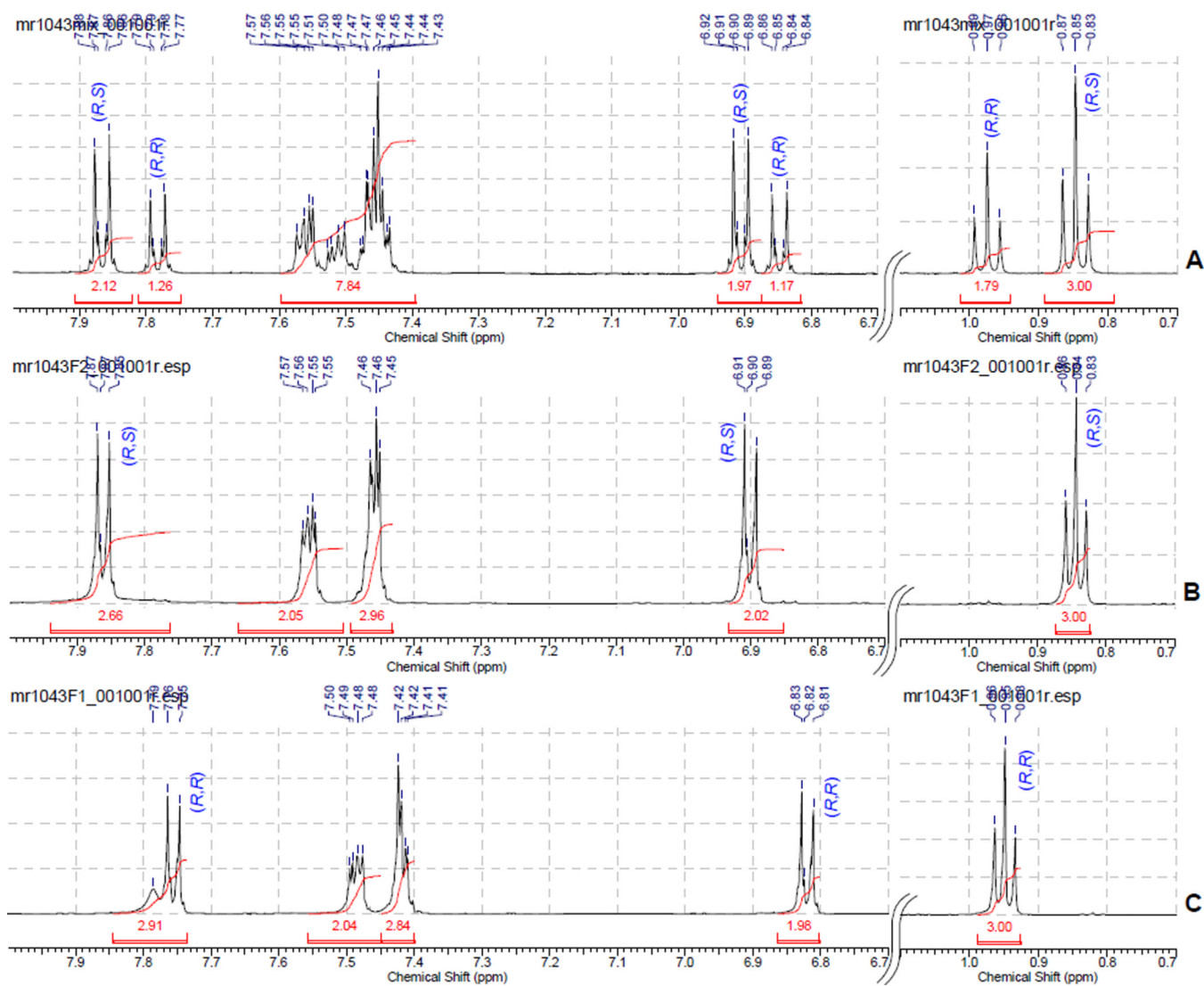


Figure 5. Fragments of ^1H NMR charts used for assigning of the absolute configuration of **12a,b**: (A) a 63:37 mixture of **12a** and **12b**. (B) pure **12a**. (C) pure **12b**.

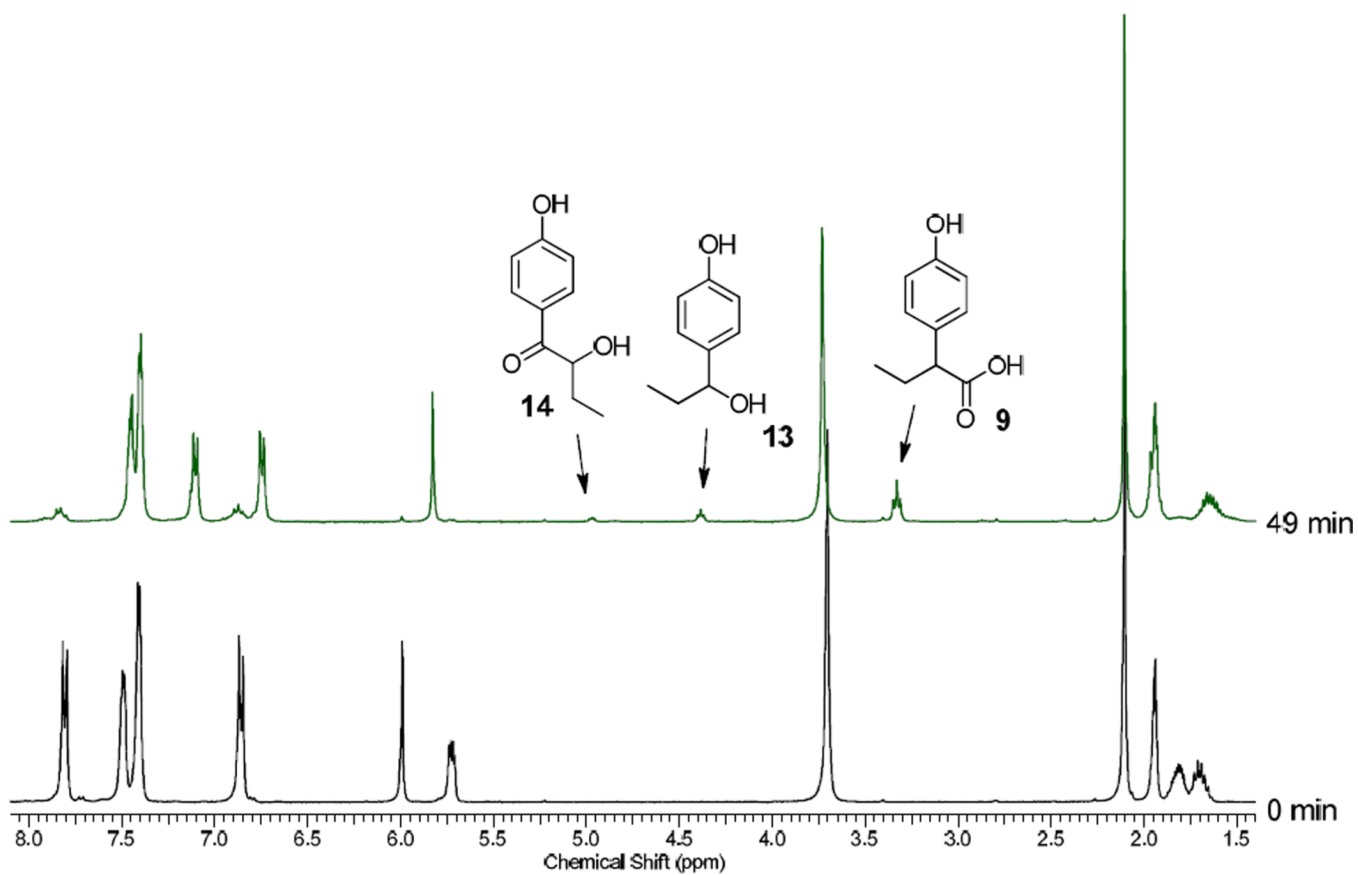


Figure 6. Photolysis of **12a** at complete conversion to products. See Discussion and Figure 2 for more detail.

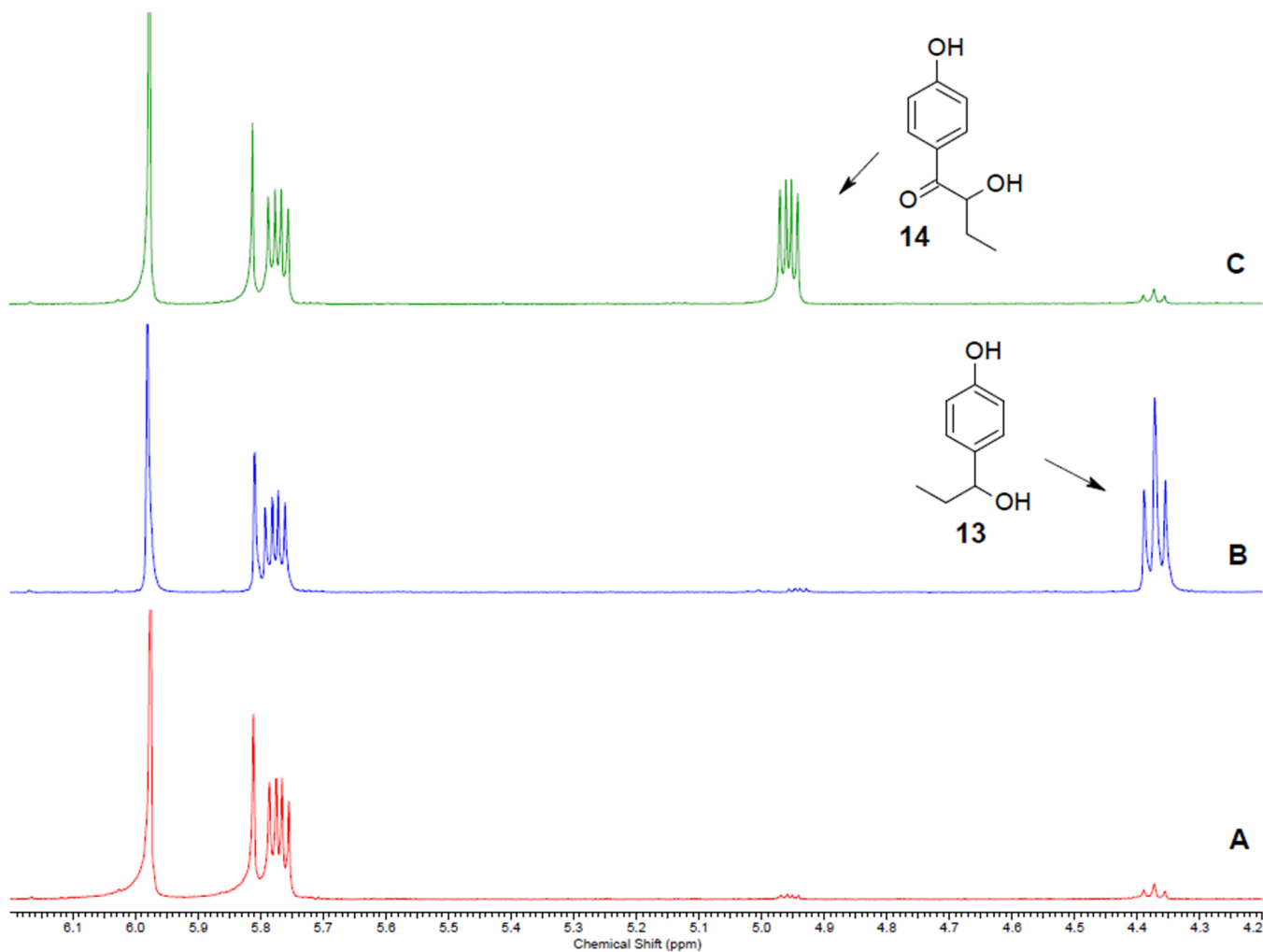
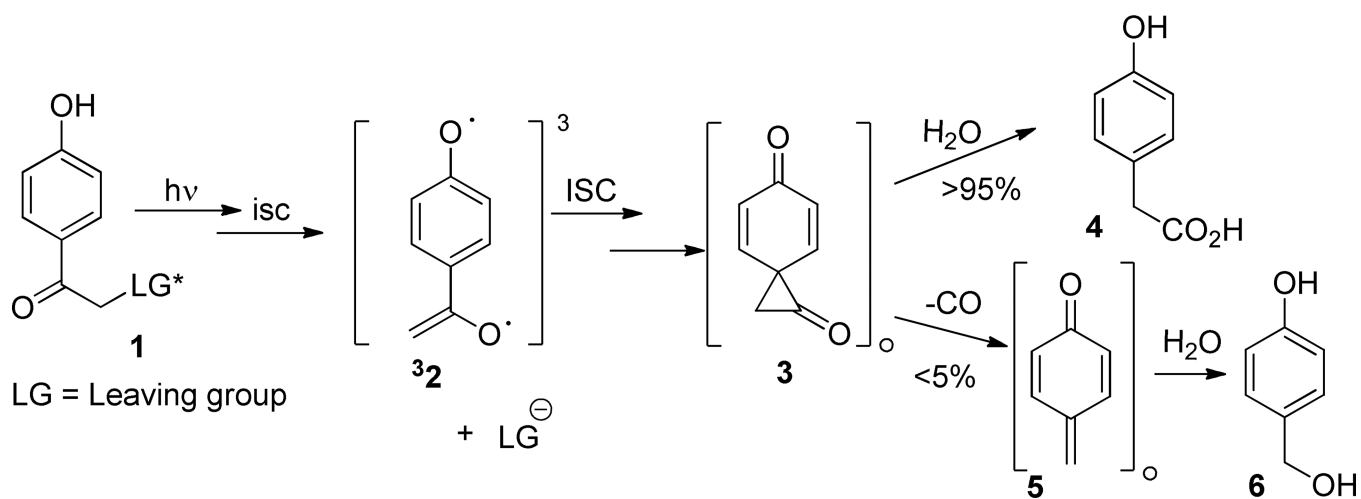
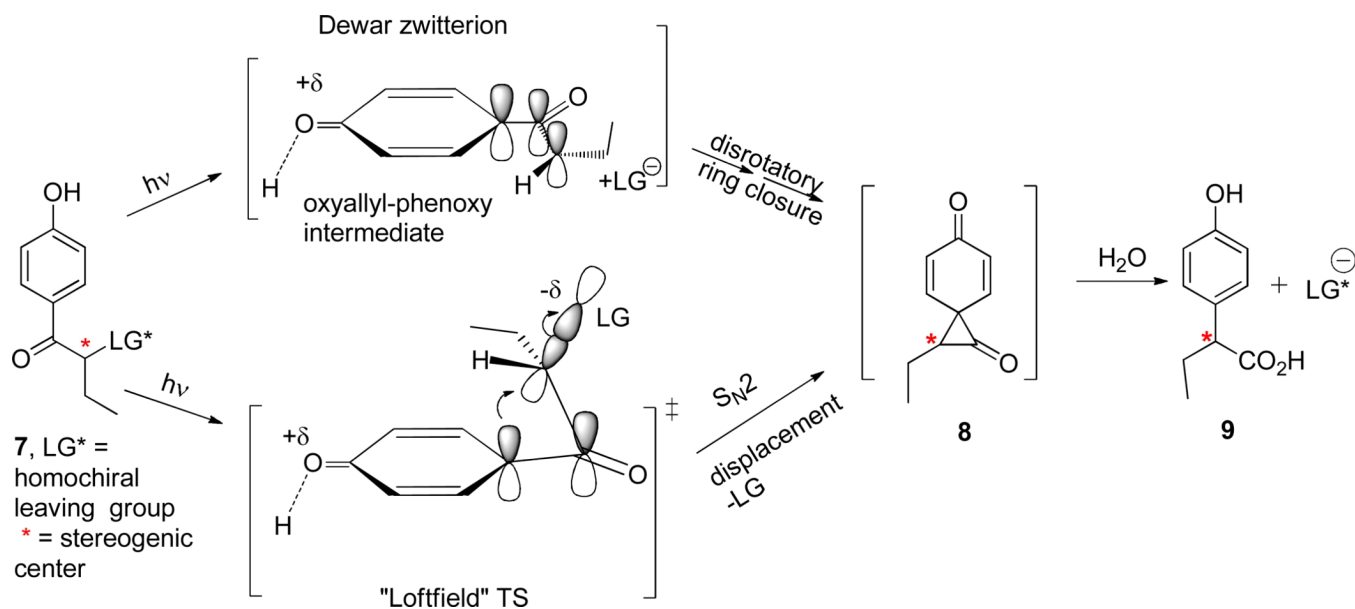


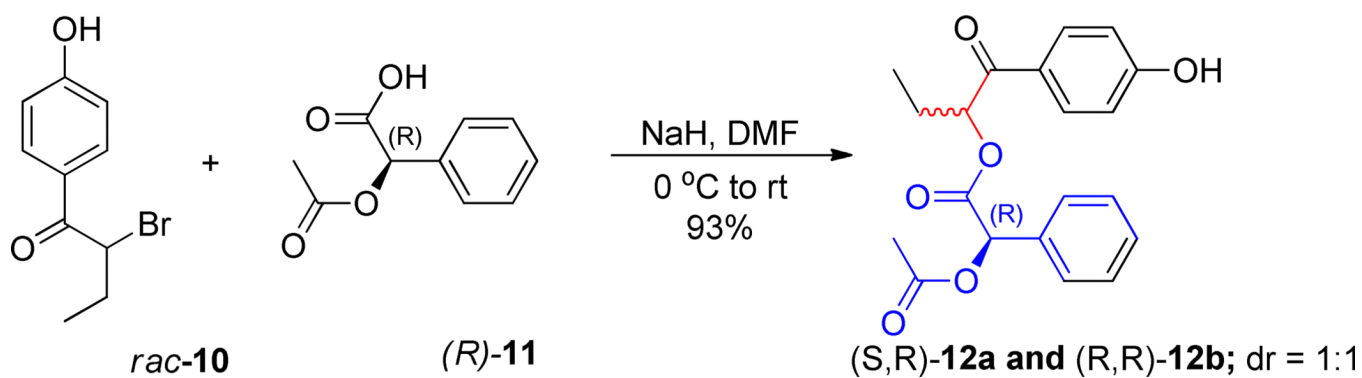
Figure 7. (A) Reaction mixture A obtained from photolysis of **12a** stopped at ~30% conversion (See Figures 2 and 6); (B) Mixture A spiked with an authentic sample of **13**; (C) Mixture A spiked with an authentic sample of **14**



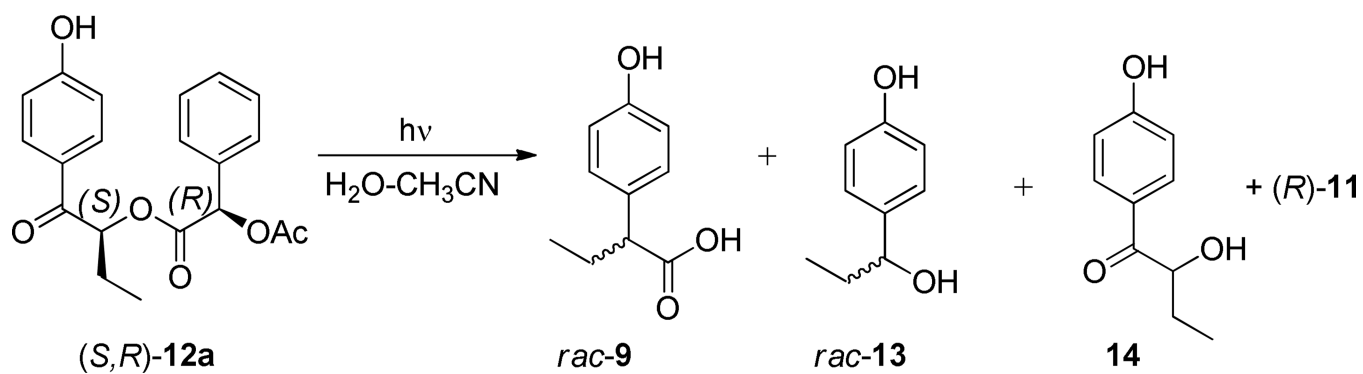
Scheme 1. General Mechanism for the photo-Favorskii Rearrangement



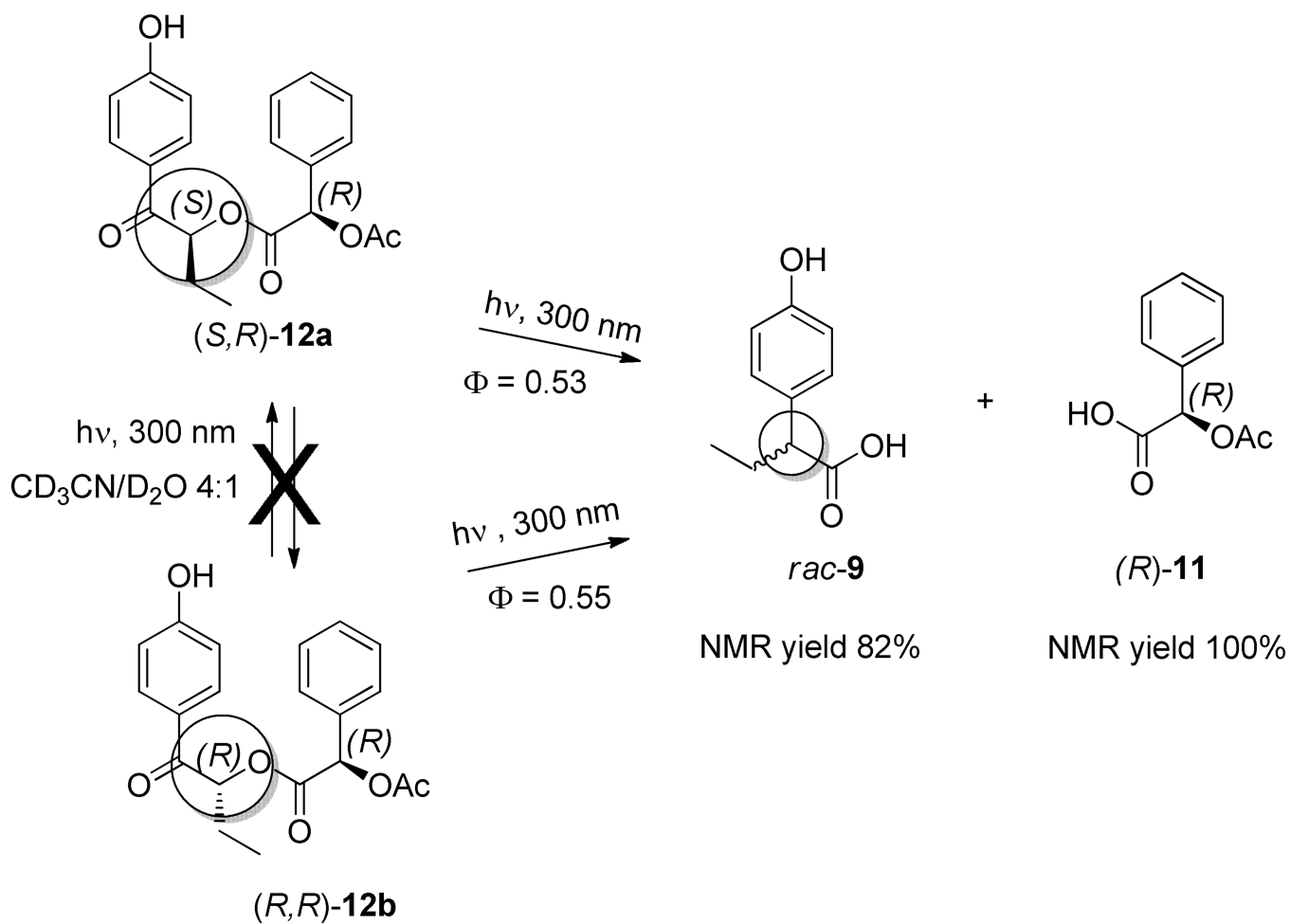
Scheme 2.
Lofield and Dewar Limiting Mechanisms as Applied to Photolysis of pHP Homologues.



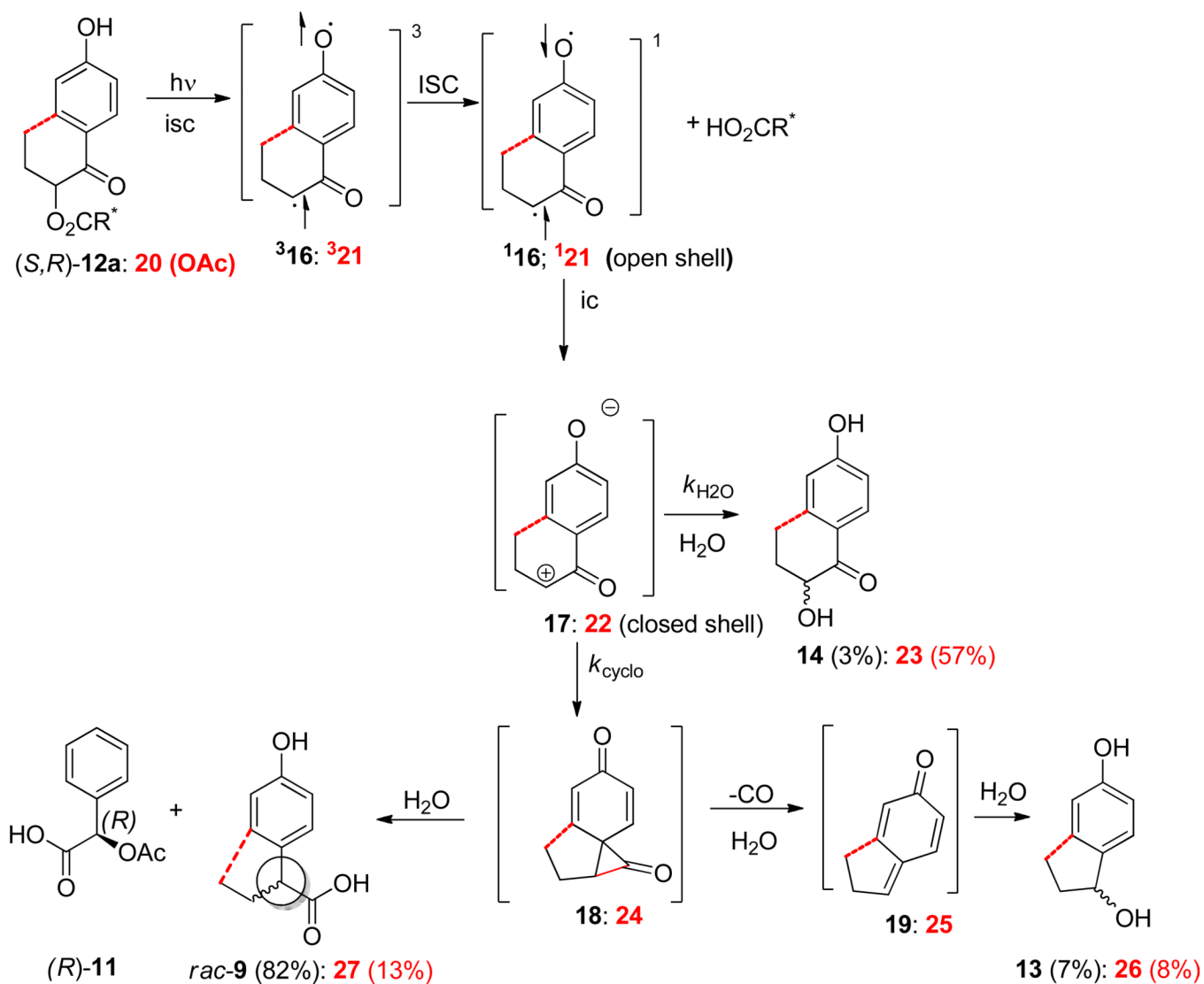
Scheme 3.
Synthesis of Diastereomeric Isomers **12a** and **12b**.

**Scheme 4.**

Photochemistry of (*S*)-1-(4-hydroxyphenyl)-1-oxobutan-2-yl (*R*)-2-acetoxy-2-phenylacetate ((*S,R*)-**12a**).



Scheme 5.
 Photochemical Integrity of the Butyrophenone Stereogenic Center of (S,R) -**12a** and (R,R) -**12b**.



Scheme 6. Contrasting and Comparing the Cyclic (20) and Acyclic (12a) *p*-Hydroxybutyrophenone Pathways