Diastereoselective synthesis and spin-dependent photodecarbonylation of di(3-phenyl-2-pyrrolidinon-3-yl)ketones: synthesis of nonadjacent and adjacent stereogenic quaternary centers†

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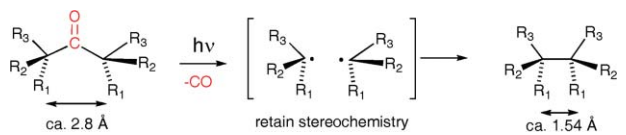
A diastereoselective procedure to obtain *N-para*-methoxybenzyl bis-α,α′-3-(3-phenyl-2-pyrrolidinone)yl substituted ketones with non-adjacent quaternary stereocenters, DL-2 and *meso*-3 was followed by a photoinduced, spin-dependent, and diastereoselective decarbonylation to give compounds DL-4 and *meso*-5, with adjacent all-carbon quaternary stereogenic centers.

Chemical structures with adjacent stereogenic quaternary carbon centers are relatively common in biologically active substances, including natural products and pharmaceuticals.[1] However, despite recent advances in synthetic methodology,[2] there are no satisfactory procedures for the preparation of this seemingly simple structural motif. The primary challenge stems from the steric impediments for six alkyl groups to converge with the precise orientation within a distance of 1.54 Å, which is the bond distance between the two adjacent carbons. To address this problem, our group has been interested in the photodecarbonylation of hexasubstituted ketones (Scheme 1).[3] With quaternary carbon distances that are longer by 80% (*ca.* 2.8 Å) and easier preparation, hexasubstituted ketones are appealing synthetic intermediates.[4] Notably, in addition to the stereocontrolled synthesis of hexasubstituted ketones, this strategy requires that the stereochemistry of the intermediate radical pair be preserved and we have shown excellent results when reactions are carried out in the crystalline solid state.[5]

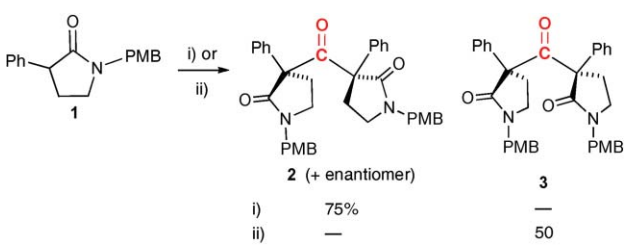
Interested in structures that occur in either *meso*- or DL- forms, we decided to explore the two-step procedure illustrated in Scheme 2, starting with 3-phenylpyrrolidine-2-one **1**. We reasoned that deprotonation followed by reaction with a carbonyl equivalent might form the desired hexasubstituted ketones in a diastereoselective manner. We selected phenylpyrrolidinone **1** with the expectation that the resulting ketones **2** and **3** would react efficiently as a result of the radical stabilizing abilities of their α-phenyl and α-carbonyl substituents.[3] Compound **1** also possesses the aryl, carbonyl and nitrogen functionalities that are common to many alkaloids, and should be valuable to determine the applicability of the solid-state reaction for the synthesis of complex natural products.[6] In this communication, we report the stereoselective preparation of the DL- and *meso*-ketones **2** and **3** and their unexpectedly selective solution photochemistry.



Scheme 1 Synthesis of all-carbon quaternary centers by photodecarbonylation of hexasubstituted ketones.

Compound **1** was prepared by *para*-methoxybenzyl (PMB) protection of the free amide obtained by the method of Michael *et al.* from diethyl 2-phenylmalonate.[7] As indicated in Scheme 2, formation of the lithium enolate of **1** with LiHMDS in THF at −78 °C followed by addition of 0.5 eq. of $COCl_2$ and warming up to *ca.* −40 °C gave the DL-pair **2** as the only detectable product in 75% isolated yield. Alternatively, reaction of the same enolate with 1,1-carbonyl diimidazolide (CDI) from −110 to −60 °C provided the *meso*-diastereomer **3** along with several unidentified byproducts. Reactions with $COCl_2$ were monitored by TLC and allowed to proceed until the starting material **1** was completely consumed, typically within 2 h. Reactions with CDI were optimized for a yield of **3** of *ca.* 45–50%, which gave some unreacted starting material and several unidentified products. After establishing the isomeric nature of **2** and **3** by mass spectrometry, ^1H and ^{13}C NMR, their relative stereochemistry was assigned with help of single-crystal X-ray diffraction analysis of **3**,‡ which turned out to be the *meso*-diastereomer (Fig. 1). Notably, compound **3** adopts a non-symmetric C_1 conformation with the two phenyl substituents adopting the two sides of the plane of the carbonyl group.

The results in Scheme 2 depend strongly on the conditions indicated. Experiments carried out with NaH, NaHMDS and KH did not give the desired ketones. Only starting material and unidentified products were obtained. However, experiments with NaHMDS and 10–20 eq. of LiCl yielded the desired products,



Scheme 2 *Reagents and conditions*: (i) LiHMDS, then 0.5 eq. $COCl_2$ (−78 to −40 °C), THF; (ii) LiHMDS, then 0.5 eq. CDI (−110 to −60 °C), THF.

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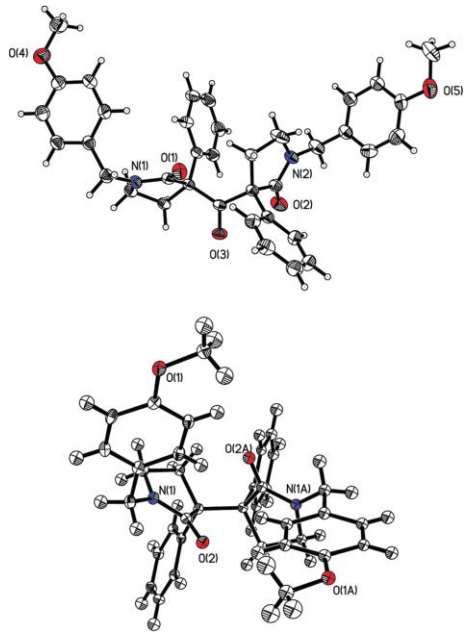


Fig. 1 (Top) ORTEP diagram of ketone *meso*-**3** (298 K) and (bottom) decarbonylation product DL-**4** (100 K). Compound **4** crystallizes in a conformation with C_2 symmetry and is viewed down the twofold axis across the central C–C bond. Both structures are shown at the 30% probability level.

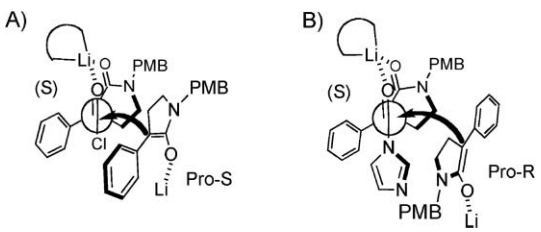
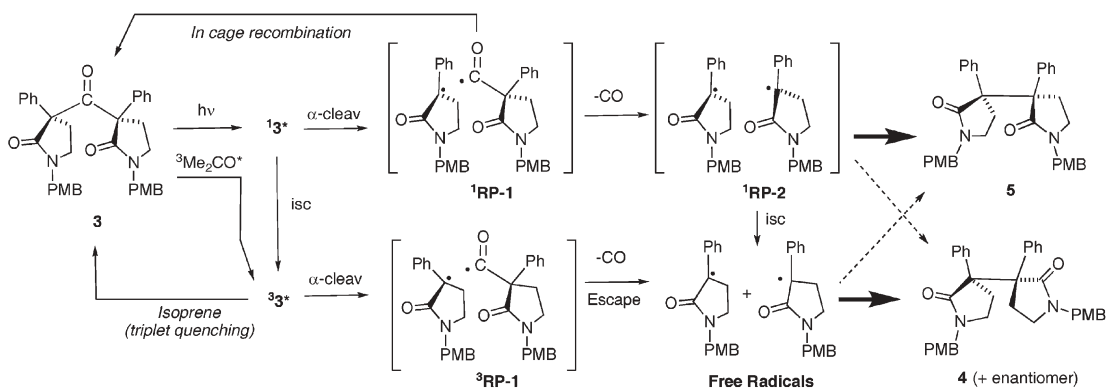


Fig. 2 Possible reaction trajectories showing the preferred face attack on the (*S*)-enantiomer of both acyl chloride and acyl imidazolide intermediates.

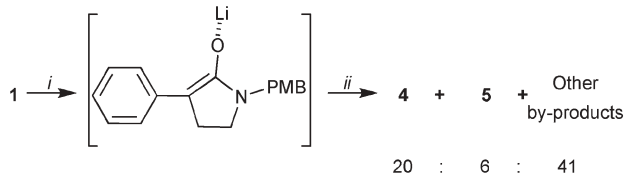
suggesting that Li^+ chelation is essential. There was no changes in diastereoselectivity with a large excess of LiCl using LiHMDS, suggesting that chelation of the 1,3-dicarbonyl is needed, but that lithium-mediated aggregates of the electrophile and nucleophile may not be involved. The formation of ketones **2** and **3** occurs by intermediacy of an acyl chloride in the case of $COCl_2$, and an acyl imidazolide in the case of CDI. Two possible reaction trajectories leading to the observed products with a lithium-chelated (*S*)-enantiomer of the acyl chloride (A) and acyl imidazolide (B) and approaching nucleophiles, respectively, are illustrated in Fig. 2. Structure A has the lithium enolate approaching the acyl chloride with the required *si*-face to form one of the enantiomers of the DL-pair. Structure B accounts for the *meso*-diastereoselectivity when the larger imidazolide ion is the leaving group. We speculate that adverse steric interactions between phenyl and imidazolyl groups and the preferred orientation of the enolate oxygen may cause the enolate to flip and rotate to expose the re-face. Positioning the phenyl group of the enolate in B close to the pyrrolidinone, which would have been avoided in A, would account for longer reaction times, more side products, and the lower yield of the meso diastereomer **3**.

After establishing the diastereoselective synthesis of **2** and **3** we set out to investigate their photochemical reactivity in solution. Experiments were carried out in deoxygenated 0.1 M benzene solutions using a Hanovia medium pressure Hg lamp with $\lambda >$ 280 nm (Pyrex filter). Two major products obtained in 60–80% were identified as the expected decarbonylation and radical–radical combination products **4** and **5** (Scheme 3). Both have a molecular ion M^+ corresponding to the loss of CO from the starting ketones, and their ^1H and ^{13}C NMR were consistent with the dynamically averaged C_s and C_2 symmetries of the *meso*- and DL-pair, respectively. The stereochemical identities of **4** and **5** were established with the help of single-crystal X-ray diffraction of DL-**4** (Fig. 1, bottom).‡

Remarkably, while irradiation of ketone **2** gave compounds **4** and **5** in 40 and 20% isolated yields, respectively, the yields from ketone **3** switched to 26 and 63%. Unexpectedly, they both display a *ca.* 2 : 1 tendency to retain the stereochemistry of the reactant in the product, requiring a mechanism with stereochemical memory. While concerted CO extrusions have been considered in the literature, there have been no conclusive examples reported.[8] A more likely mechanism involves a singlet state α-cleavage, loss of CO, and rapid recombination of the singlet radical pair to preserve the stereochemistry of the reactant. In fact, stereospecific reactions of singlet radical pairs have been reported in the literature in the photo-Claisen reaction[9] and decarboxylative photocyclizations.[10] In order to establish the stereochemical preferences of freely



Scheme 3 Proposed reaction scheme to account for the spin-selective diastereoselectivity of ketone **3**. A similar scheme applies to **2**.



Scheme 4 *Reagents and conditions*: (i) 5 eq. LiHMDS, −78 °C, 0.5 h, THF; (ii) 5 eq. $CuBr_2$, 2 h. −78 to rt.

diffusing 3-phenylpyrrolidinone-3-yl radicals, we explored the triplet-sensitized photoreactivity of **2** and **3** using acetone as the solvent and sensitizer.[11] In parallel experiments, after each reactant was consumed, the DL-compound **4** was obtained as the major product (*ca.* 50%) with only small amounts of the *meso* isomer (<5%).[12] Experiments carried out with **3** dissolved in isoprene, a well-known triplet quencher,[13] were completely stereospecific, providing **5** as the only product. A kinetic scheme that accounts for the proposed spin-selective reactivity is illustrated in Scheme 3 with *meso*-**3** as the reactant.

As illustrated in Scheme 3, the singlet radical pair ^{1}RP-1 preferentially formed upon direct irradiation must lose CO before rotation within the solvent cage so that ^{1}RP-2 may form the new σ bond without losing the stereochemistry of the reactant. Given that the decarbonylation of substituted phenylacetyl radicals is exothermic, the reversible formation of ^{1}RP-1 from caged ^{1}RP-2 and CO is very unlikely.[14] When acetone is used as the triplet sensitizer, α-cleavage from ^{3}**3** produces the triplet radical pair ^{3}RP-1, which loses CO and diffuses apart to form free radicals. Although the extent of stereoselectivity often decreases in the triplet manifold,[15] free radicals formed from either ketone diastereomer experience a high double induction and a tendency to form DL-**4**. Additional evidence for the proposed mechanism comes from the effect of isoprene, which quenches the triplet ketone, prevents the formation of free radicals, and renders the reaction of **3** almost completely stereospecific to **5**. Furthermore, quantum yield measurements at λ = 300 nm with 0.02 M solutions in deoxygenated benzene using valerophenone actinometry[16] gave values of $\Phi_{\mathbf{2}\rightarrow\mathbf{4}} \approx 0.05$ and $\Phi_{\mathbf{3}\rightarrow\mathbf{5}} \approx 0.005$, which are suggestive of a very large fraction of ^{1}RP-1 returning to the starting ketone. The differences in efficiency between the two diastereomers suggest that recombination to the starting ketone is about 10 times less likely for the DL-RP-1 as compared to *meso*-RP-1, which is consistent with the high selectivity shown by free radicals which form DL-**4** in preference of *meso*-**5**. Further evidence was obtained by investigating the coupling of the free radicals produced by oxidation of the enolate of **1**,[17] which yielded the DL-isomer **4** with a 10 : 3 preference over the *meso*-isomer **5** (Scheme 4).

In conclusion, with phenylpyrrolidinone as a starting material this study expands on a new method to obtain structures with non-adjacent (**2** and **3**) and adjacent (**4** and **5**) quaternary stereogenic centers in a highly diastereoselective manner. To the best of our knowledge, this is the first case involving photodecarbonylations *via* the Norrish type I mechanism with a high diastereoselectivity that can be controlled by accessing different spin multiplicities of the excited state. Experimental and theoretical studies are in progress to establish the source of the diastereoselectivity of ketone formation. Photochemical studies in crystals are also being investigated to determine their advantages and limitations as compared to solution reactions.

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Notes and references

‡ *Crystal data* for ketone **3** at 298(2) K: $C_{37}H_{36}N_2O_5$, M = 588.68, monoclinic, space group $P2_1/c$, a = 15.4881(18), b = 10.8020(12), c = 19.017(2) Å, β = 104.87(10)°, V = 3075.0(6) Å^3, Z = 4, D_c = 1.263 Mg m^{-3}, F(000) = 656, λ = 0.71073 Å, μ(Mo-Kα) = 0.350 mm^{-1}, crystal size = 0.20 × 0.20 × 0.05 mm; of the 7275 reflections collected, 4340 (R_{int} = 0.0189) were independent reflections; max./min. residual electron density 0.261/−0.209 e Å^{-3}, $R1$ = 0.0447 ($I > 2\sigma(I)$) and $wR2$ = 0.0901. *Crystal data* for compound **5** at 100 K: $C_{36}H_{36}N_2O_4$, M = 560.67, monoclinic, space group $C2/c$, a = 18.277(6), b = 10.860(6), c = 16.533(8) Å, β = 116.358(7)°, V = 2940(2) Å^3, Z = 4, D_c = 1.266 Mg m^{-3}, F(000) = 656, λ = 0.71073 Å, μ(Mo-Kα) = 0.350 mm^{-1}, crystal size = 0.20 × 0.10 × 0.10 mm; of the 3301 reflections collected, 2034 (R_{int} = 0.0189) were independent reflections; max/min residual electron density 0.261/−0.209 e Å^{-3}, $R1$ = 0.0447 ($I > 2\sigma(I)$) and $wR2$ = 0.0901. CCDC 656274 and 656275. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b711786h

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