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Solvent-Free Synthesis

Parallel Syntheses of (+)- and (−)-α-Cuparenone by Radical Combination in Crystalline Solids**

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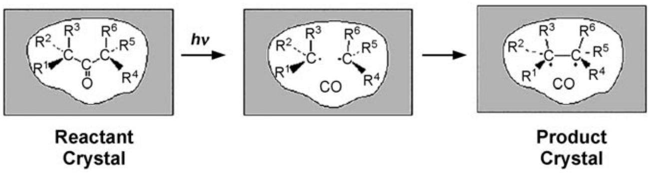
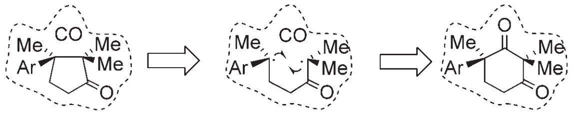
Among the forces shaping the future of organic synthesis is the drive for environmentally friendly processes in keeping with the principles of green chemistry.[1] Strategies under development include the engineering of microorganisms and enzymes,[2] the application of efficient catalysts[1,3] and environmentally friendly solvents,[4] and whenever possible, the use of chemical processes without solvents.[5,6a] It is also expected that photochemical reactions will play an important role in the synthesis of natural products and specialty chemicals.[6,7] A promising reaction in this context is the solvent-free photodecarbonylation of crystalline ketones (Scheme 1).[6a,8] While the reaction is ideal for the synthesis of molecules with adjacent quaternary stereogenic centers,[9] its application for the synthesis of enantiomerically pure natural products has not been demonstrated.[10,11] With that in mind, we report here a very efficient synthesis of the natural product (α)-cuparenone (**1**), in which the two quaternary centers are formed in the crystalline state with complete stereocontrol (Scheme 2).



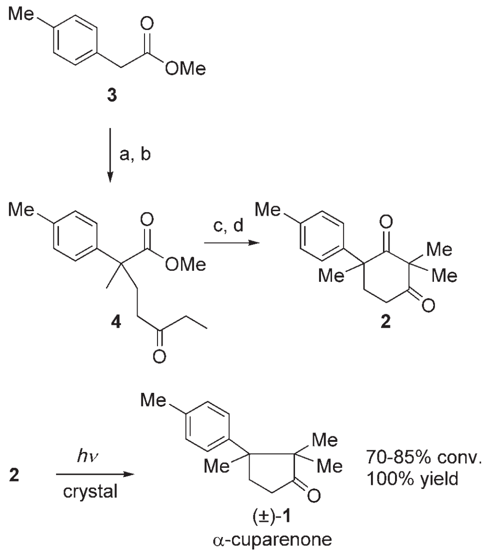
Scheme 1. Hexasubstituted acetones with radical-stabilizing substituents at both α carbons react photochemically in the crystalline state to generate radical pairs that bond to form adjacent quaternary stereogenic centers in a highly stereospecific process.



1 **2**

Scheme 2. Retrosynthesis of (α)-cuparenone (**1**) by stereospecific solid-state photodecarbonylation of diketone **2**. The dotted line represents the reaction cavity; Ar = 4-MeC$_6$H$_4$.

(α)-Cuparenone (**1**) is a crystalline compound and a suitable candidate for a solid-to-solid photochemical reaction. (*S*)-(+)-(α)-Cuparenone was first isolated from the wood of the Mayur Pankhi in 1964[12] and (*R*)-(−)-(α)-cuparenone from the liverwort *Mannia fragrans* in 1976.[13] With two adjacent quaternary centers, one of which is stereogenic, (α)-cuparenone has been one of the most sought-after targets to test novel methodologies, thus providing a good standard for comparison.[14] As a starting point, we prepared racemic cyclohexanedione (±)-**2** in four simple steps in 59.7 % overall yield from methyl 2-tolyl-acetate (**3**) (Scheme 3). Clear prisms of (±)-**2** (m.p. 63.0–65.5 °C) obtained from hexane were suitable for photochemical studies.



Scheme 3. a) KH, MeI, THF, 0 °C, 92 %; b) LDA, ethyl vinyl ketone, THF, 0 °C, 81 %;c) Na, MeOH, reflux, 99 %; d) KH, MeI, DMF, 75 °C, 81 %.

Irradiation of (±)-**2** in degassed 0.1 M benzene solutions with a medium-pressure Hg Hanovia lamp using a Pyrex filter ($\lambda > 290$ nm) gave (±)-(α)-cuparenone in 34 % yield along with several other products after 100 % percent conversion.[15] In contrast, irradiation of (±)-**2** in powder form (20 mg) at −20 °C yielded (±)-(α)-cuparenone as the only product at 70 % conversion. Larger samples (0.1 g) conveniently irradiated at ambient temperature as nanocrystalline suspensions[16–18] provided (±)-α-cuparenone in 85 % yield.

To prepare the enantiomerically pure natural products we carried out a classical resolution of (±)-**2** via the diastereo-

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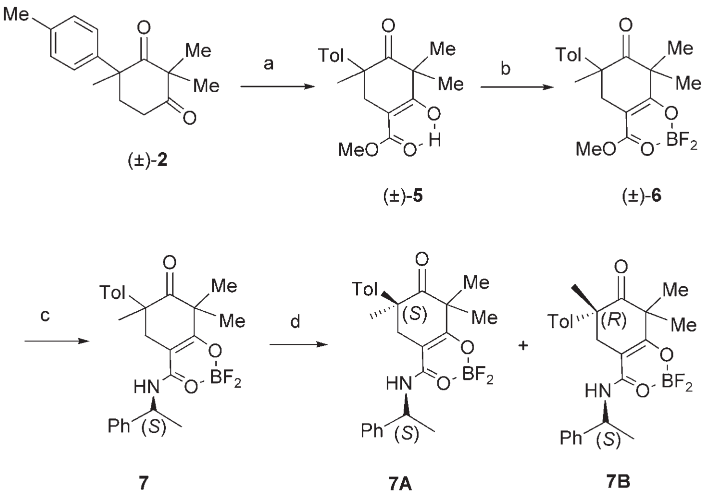
meric difluorodioxaborinane complexes of β-keto-(*S*)-(α)-methylbenzylamide (**7**) (Scheme 4)[19] β-Ketoester (±)-**5** was obtained in 92% yield by selective C-acylation of (±)-**2** with methyl cyanoformate, and subsequent treatment with



Scheme 4. a) LiHMDS, MeO(CO)CN, 92%; b) BF_3OEt_2, toluene, 100%; c) (*S*)-(α)-methylbenzylamine, MeCN, 80%; d) silica gel chromatography (EtOAc/hexane 2:8). LiHMDS = lithium hexamethyldisilylazide.

BF_3OEt_2 gave difluorodioxaborinane (±)-**6** in > 98% yield. Reaction of (±)-**6** with (−)-(*S*)-(α)-methylbenzylamine in acetonitrile yielded 80% of diastereomers **7**. Separation by column chromatography (EtOAc/hexane 2:8) led to pure **7A** and **7B**, with R_f values of 0.4 and 0.3, respectively. Crystallization from ether gave **7A** and **7B** as colorless X-ray-quality needles (224–227 °C) and platelike crystals (192–198 °C), respectively.

Since we knew that the absolute configuration of the (α)-methylbenzylamine enantiomer used is *S*, we could determine by single-crystal X-ray diffraction analysis[20] that the quaternary carbon of **7A** also has the *S* configuration (Figure 1). With the (*S*,*S*)-**7** configuration assigned to the less polar diastereomer **A**, the configuration of the more polar isomer was assigned as (*S*,*R*)-**7**. Optical rotation measurements revealed $[\alpha]_D^{23}$ ($c = 0.25$) values of +60° and −237°, for (+)-(*S*,*S*)-**7** and (−)-(*S*,*R*)-**7**, respectively. Circular dichroism in CH_2Cl_2 displayed approximately opposite Cotton effects with different intensities in the region of 220–350 nm (see the Supporting Information).

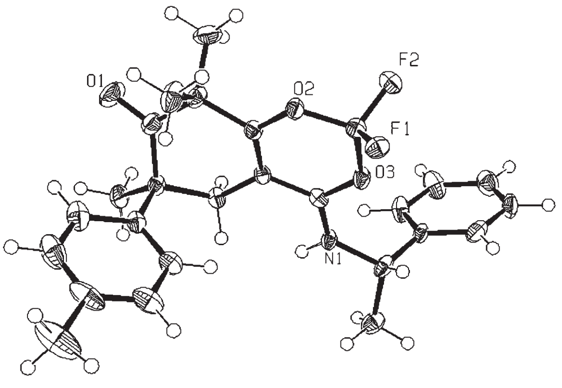
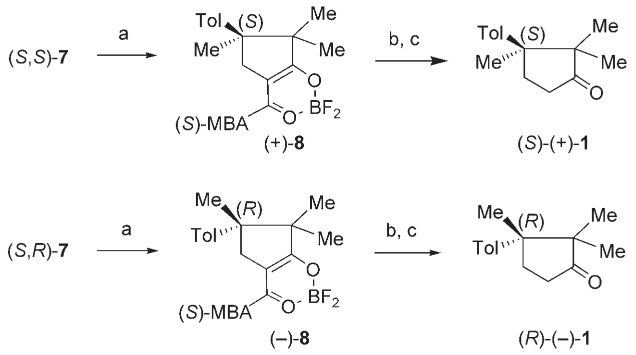


Figure 1. X-ray structure of the less polar diastereomer, **7A**, shown to have the absolute configuration (*S*,*S*)-**7**; ellipsoids at the 30% probability level.

Removal of the chiral auxiliary from (+)-(*S*,*S*)-**7** exposed one of the limitations of solid-state photochemistry. Samples of (−)-(*S*)-**2** ($[\alpha]_D^{20}$ ($c = 1$) = −35°)[21] failed to crystallize under a wide variety of experimental conditions, and solid-state irradiation could not be carried out. Solution irradiation of (−)-(*S*)-**2**, as expected, gave low yields of the desired product with complete racemization. Nonetheless, the syntheses of (+)- and (−)-(α)-cuparenone were completed by taking advantage of the high melting points of the ketoamide complexes **7**. Parallel UV/Vis irradiation of suspended nanocrystals of (+)-(*S*,*S*)-**7** and (−)-(*S*,*R*)-**7** (100 mg) in aqueous cetyltrimethylammonium bromide (CTAB) solutions led to the clean formation of the (α)-cuparenone ketoamide derivatives (+)-(*S*,*S*)-**8** and (−)-(*S*,*R*)-**8** with 100% stereoselectivity in 80% yield (Scheme 5).[22] Removal of the BF_2 unit with NaOAc in ethanol followed by amide hydrolysis and decarboxylation gave the the two natural products each in 90% yield. The optical rotation of the two final products matched the values reported in the literature[23,24] and the CD spectra display a perfect mirror-image relation with maxima at 300 nm (see the Supporting Information).



Scheme 5. a) *hν*, suspension of nanocrystals in aq. CTAB solution, 80%; b) $MeCO_2Na$, EtOH, 70 °C, > 98%; c) 6.0 M HCl, 100 °C, 90%. CTAB = cetyltrimethylammonium bromide; MBA = methyl benzyl amine.

Previous syntheses of (α)-cuparenone range from 3 to 15 steps for racemic samples and from 7 to 20 steps for the enantiomerically enriched natural product (see the Supporting Information). The highest overall yields are 56% for the racemic sample and 29% (96.5% *ee*) for (−)-(α)-cuparenone.[14] Using a photochemical solid-to-solid reaction as the key step, we report here the total synthesis of (±)-(α)-cuparenone in four steps and 60% overall yield. For the parallel synthesis of the two enantiomerically pure natural products, five reactions and one diastereomeric separation starting from (±)-**2** led to (*S*)-(+)-**1** and (*R*)-(−)-**1** in 100% *ee* and 52% total yield (26% of each pure enantiomer).

In conclusion, the photoinduced decarbonylation of crystalline hexasubstituted ketones offers a very simple approach for the stereospecific synthesis of natural products with adjacent stereogenic quaternary centers. With higher yields, fewer steps, ideal selectivities, and easy scaleup, solid-to-solid reactions may have a strong impact on natural product synthesis and green chemistry.

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[14] Roughly 20 racemic and 17 asymmetric syntheses have been reported. For number of steps, yields, and references, please consult the Supporting Information.

[15] Identifiable byproducts include 12% 2-tolyl-6-methyl-5-oxo-1-heptene and 4% 2-methyl-6-tolyl-3-xo-1-heptene formed by radical disproportionation.

[16] Stable suspensions were prepared by the reprecipitation method (Ref. [17]), by addition of a saturated solution of (±)-**2** in acetone into a vigorously stirred aqueous CTAB solution five times below its critical micelle concentration of $1.6\times10^{-4}\,\text{M}$ (L. Sepulveda, J. Cortes, *J. Phys. Chem.* **1985**, *89*, 5322–5324).

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[20] X-ray data for (S,*S*)-**7**: $C_{25}H_{28}BF_2NO_3$, colorless plates, $M_w = 439.29$, monoclinic, space group $P21$, $a = 11.5147(18)$, $b = 13.938(2)$, $c = 14.577(2)$ Å, $\beta = 100.418(3)$, $Z = 4$, F_000 = 928, $\lambda = 0.71073$, $T = 100(2)$, crystal dimensions $= 0.4\times0.2\times0.15\ \text{mm}^3$, $R_1 = 0.0439$, $wR_2 = 0.0783$ (all data). CCDC 635860 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] The sign of optical rotation of the enantiomers of diketone **2** is opposite to that of the diketoamides **7**, ketoamides **8**, and cuparenones **1** with the same absolute configuration at the quaternary carbon.

[22] While photoreaction of (+)-(*S*,*S*)-**7** and (−)-(*S*,*R*)-**7** as a nanocrystalline suspension selectively gave (+)-(*S*,*S*)-**8** and (−)-(*S*,*R*) **8**, respectively, photoreactions in solution gave a mixture of diastereomers.

[23] Based on crystal structure, optical rotation, and CD analysis of (*S*,*S*)-**7** and those of the natural products, we confirmed the *R* and *S* configurations for the *levorotatory* and dextrorotatory isomers, respectively.

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