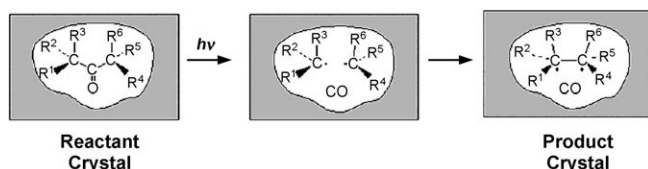


Solvent-Free Synthesis

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

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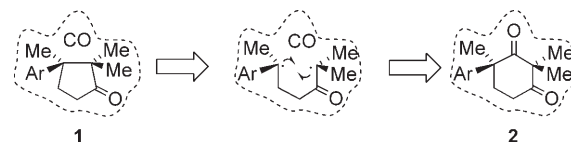
Among the forces shaping the future of organic synthesis is the drive for environmentally friendly processes in keeping with the principles of green chemistry.^[1] Strategies under development include the engineering of microorganisms and enzymes,^[2] the application of efficient catalysts^[1,3] and 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



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.

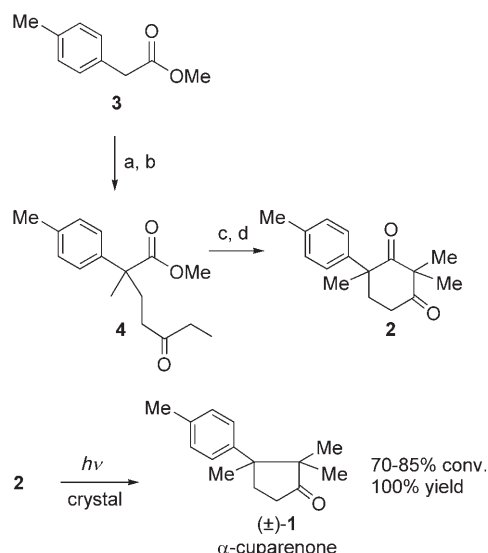
of molecules with adjacent quaternary stereogenic centers,^[9] its application for the synthesis of enantiomerically pure natural products has not been demonstrated.^[10,11] With that in mind, we report here a very efficient synthesis of the natural product (α)-cuparenone (**1**), in which the two quaternary centers are formed in the crystalline state with complete stereocontrol (Scheme 2).

(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



Scheme 2. Retrosynthesis of (α)-cuparenone (**1**) by stereospecific solid-state photodecarbonylation of diketone **2**. The dotted line represents the reaction cavity; Ar = 4-MeC₆H₄.

test novel methodologies, thus providing a good standard for comparison.^[14] As a starting point, we prepared racemic cyclohexanedione ($\pm$)-**2** in four simple steps in 59.7% overall yield from methyl 2-tolyl-acetate (**3**) (Scheme 3). Clear prisms of ($\pm$)-**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 ($\pm$)-**2** in degassed 0.1M benzene solutions with a medium-pressure Hg Hanovia lamp using a Pyrex filter ($\lambda > 290$ nm) gave ($\pm$)-(α)-cuparenone in 34% yield along with several other products after 100% percent conversion.^[15] In contrast, irradiation of ($\pm$)-**2** in powder form (20 mg) at −20°C yielded ($\pm$)-(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 ($\pm$)- α -cuparenone in 85% yield.

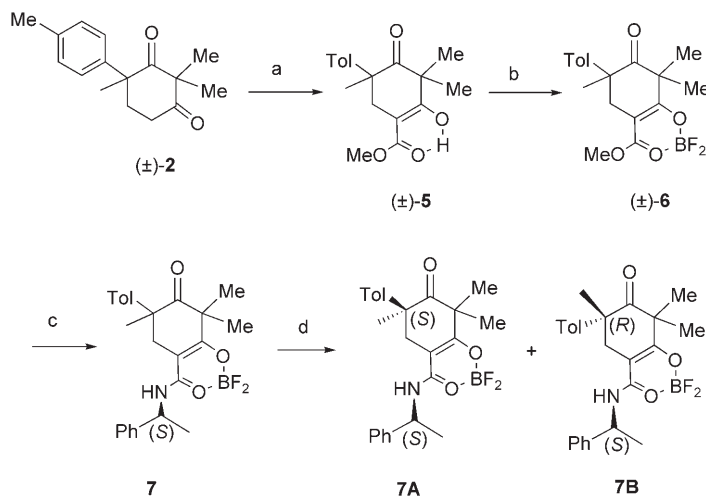
To prepare the enantiomerically pure natural products we carried out a classical resolution of ($\pm$)-**2** via the diastereo-

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



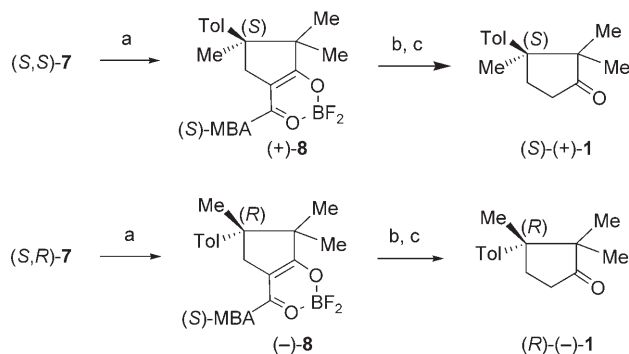
Scheme 4. a) LiHMDS, MeO(CO)CN, 92%; b) BF₃OEt₂, toluene, 100%; c) (*S*)-(α)-methylbenzylamine, MeCN, 80%; d) silica gel chromatography (EtOAc/hexane 2:8). LiHMDS = lithium hexamethyldisilylazide.

BF₃OEt₂ gave difluorodioxaborinane ($\pm$)-**6** in > 98 % yield. Reaction of ($\pm$)-**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 [α]_D²³ (*c* = 0.25) values of +60° and –237°, for

(+)-(*S,S*)-**7** and (–)-(*S,R*)-**7**, respectively. Circular dichroism in CH₂Cl₂ displayed approximately opposite Cotton effects with different intensities in the region of 220–350 nm (see the Supporting Information).

Removal of the chiral auxiliary from (+)-(*S,S*)-**7** exposed one of the limitations of solid-state photochemistry. Samples of (–)-(*S*)-**2** ([α]_D²⁰ (*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 BF₂ unit with NaOAc in ethanol followed by amide hydrolysis and decarboxylation gave 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



Scheme 5. a) *hν*, suspension of nanocrystals in aq. CTAB solution, 80%; b) MeCO₂Na, EtOH, 70 °C, > 98%; c) 6.0 M HCl, 100 °C, 90%. CTAB = cetyltrimethylammonium bromide; MBA = methyl benzyl amine.

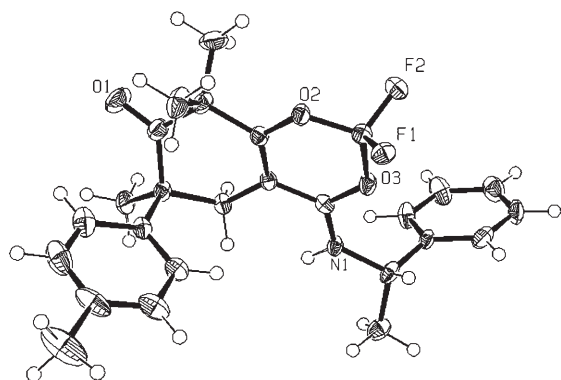


Figure 1. X-ray structure of the less polar diastereomer, **7A**, shown to have the absolute configuration (*S,S*)-**7**; ellipsoids at the 30 % probability level.

the CD spectra display a perfect mirror-image relation with maxima at 300 nm (see the Supporting Information).

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 ($\pm$)-(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 ($\pm$)-**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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- [22] While photoreaction of (+)-(S,S)-**7** and (–)-(S,R)-**7** as a nano-crystalline suspension selectively gave (+)-(S,S)-**8** and (–)-(S,R)-**8**, respectively, photoreactions in solution gave a mixture of diastereomers.
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