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

Arunkumar Natarajan, Danny Ng, Zhe Yang, and Miguel A. Garcia-Garibay*

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

 [*] Dr. A. Natarajan, D. Ng, Z. Yang, Prof. Dr. M. A. Garcia-Garibay Department of Chemistry and Biochemistry University of California, Los Angeles
 607 C.E. Young Drive East, Los Angeles, CA 90095-1569 (USA) Fax: (+1) 310-825-3159
 E-mail: mgg@chem.ucla.edu

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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 $(\lambda > 290 \text{ nm})$ 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



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.

(+)-(*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).

Removal of the chiral auxiliary from (+)-(S,S)-7 exposed one of the limitations of solid-state photochemistry. Samples of (-)-(S)-2 $([\alpha]_D^{20} (c=1) =$ $(-35^{\circ})^{[21]}$ 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) $h\nu$, 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.

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).

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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, solidto-solid reactions may have a strong impact on natural product synthesis and green chemistry.

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- [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.
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