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Total Synthesis of (±)-Herbertenolide by Stereospecific Formation of Vicinal Quaternary Centers in a Crystalline Ketone

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

Department of Chemistry and Biochemistry, University of California—Los Angeles, Los Angeles, California 90095-1569
mgg@chem.ucla.edu

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ABSTRACT

The sesquiterpene (±)-herbertenolide was synthesized in seven steps from commercial 2-bromo-4-methylanisole. In the key step, two adjacent stereogenic quaternary centers were controlled by a highly chemoselective and stereospecific photodecarbonylation reaction of crystalline methyl-trans-3-(2-methyl-5-methoxyphenyl)-1,3-dimethyl-2-oxocyclohexancarboxylate (3). An efficient generation of radical pairs and the stereochemical control exerted by the solid state suggest that this reaction may become a useful synthetic method.

Strongly motivated by the potential of solvent-free procedures and the development of “green chemistry” for the synthesis of structurally challenging natural products and specialty chemicals, we have recently shown that photodecarbonylation of crystalline ketones may be a reliable and efficient method for generating biradicals and radical pairs in the solid state. We have also observed that radicals formed in such a constrained environment recombine with chemoselectivities and stereospecificities that frequently rival those observed in enzymatic processes (Scheme 1).

A critical requirement for a successful solid-state photodecarbonylation is the presence of radical stabilizing groups at the two α-carbons of the ketone. Therefore, in the past few years we have directed our efforts to the systematic exploration of suitable substituents for this purpose. We have reported that combinations of phenyl, carbonyl, alkoxy, and cyano groups allow efficient solid-state photodecarbonylation to occur. We recently disclosed the use of this

reaction as a simple and efficient method for the enantiospecific preparation of compounds with vicinal tertiary and quaternary stereocenters. In this communication, we extend the method for the synthesis of compounds with adjacent quaternary stereocenters, a common structural feature of many natural products and one of the most demanding challenges in organic synthesis. As a test case, we report a diastereospecific total synthesis of the sesquiterpene herbertanolide (1), in which the bond connecting the vicinal quaternary centers is formed in the solid state. This synthesis represents the first time that a solid-state reaction is used as a key step in the total synthesis of a natural product.

Herbertanolide (I, Scheme 2) was first isolated and characterized by Matsuo et al. from the leafy liverwort Herberta adunca, the extract of which has been shown to exhibit a remarkable growth suppression of certain plant pathogenic fungi. To date, there have been only two reported syntheses of this natural product. The two vicinal quaternary centers in its structure present an ideal platform for testing our proposed methodology. The retrosynthetic analysis outlined in Scheme 2 suggests that formation of the lactone ring should proceed spontaneously after hydrolysis of the ester and deprotection of the ether group in 2. The preparation of ester 2, which contains the target vicinal quaternary centers, may be accomplished via the stereospecific solid-state photodecarbonylation of the cyclohexanone precursor 3. As indicated in Scheme 1, the reaction starts by electronic excitation and proceeds by intersystem crossing to the triplet excited state (ISC). We have shown that a substitution pattern such as that of ester 3 can lower the bond dissociation energies of the two \( \alpha \)-bonds, thus facilitating sequential \( \alpha \)-cleavage and decarbonylation reactions within the lifetime of the triplet. As the 1,5-biradical formed in this manner is structurally trapped in the crystal lattice of its precursor, the two radical centers remain configurationally trapped until they can spin flip to the singlet state (ISC') to form the desired bond.

Even though a priori predictions of the crystallinity and melting point of 3 are impossible, the presence of the ester functional group should allow one to modify the physical properties of the precursor by changing the nature of the alkoxy substituent. The requisite trans configuration of 3 should arise from the diastereoselective acylation of the corresponding ketone precursor, prepared from 4. The synthesis of (±)-herbertanolide began with the commercially available 2-bromo-4-methylanisole (4) (Scheme 3). Lithiation of 4 with butyllithium followed by treatment with cyclohexene oxide and BF\(_3\)-Et\(_2\)O resulted in the acid-catalyzed epoxide opening to give trans-cyclohexanol 5. Oxidation of 5 under Swern conditions proceeded smoothly to give the desired 2-aryl-cyclohexanone 6 with an overall yield of 96% over two steps. After several low-yielding attempts at one-pot double-methylation of 6, a sequential two-step procedure using sodium hydride/Mel followed by LDA/Mel was found to give the best yield of 7 (60%, two steps).

Acylation of 7 was then carried out using a modification of Mander’s procedure with commercially available methyl cyanoformate (Scheme 3). Satisfyingly, the resulting methyl ester 3 was obtained in 72% yield with an excellent diastereoselectivity (>98:2). The ketoester 3 turned out to be a highly crystalline material with a mp = 96–97 °C. The desired trans stereochemistry was unambiguously established by X-ray crystallographic analysis (Figure 1), which revealed a chair conformation with the aromatic group adopting an equatorial position.

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(12) Selected crystal data: C\(_2\)H\(_2\)O\(_2\), colorless prisms, FW = 304.37 amu, space group P\(_2\)/c, \( a = 8.7539(13) \), \( b = 14.4912(2) \), \( c = 13.0722 \). \( \beta = 95.806(3) \), \( Z = 4 \). \( \rho_{calc} = 1.225 \) Mg/m\(^3\). F(000) = 656, \( \lambda = 0.71073 \) Å, \( T = 100(2) \) K, crystal size = 0.20 \( \times \) 0.30 \( \times \) 0.30 mm\(^3\). Of the 7269 reflections collected (2.10° ≤ θ ≤ 27.55°), 2915 (R(int) = 0.0208) were independent reflections; max/min residual electron density 273 and −188 e/nm\(^3\), \( R_1 = 0.0352 \), \( wR_2 = 0.0907 \) (all data).
Photochemical irradiation of 3 in 0.1 M, argon-sparged benzene solutions produced a complex mixture, later shown not to contain cyclopentane 2 (Scheme 4). The $^1$H NMR spectrum of the crude reaction mixture contained several vinylic hydrogen signals, suggesting disproportionation of the biradical intermediate as the dominant solution pathway. In contrast, the photoysis of finely powdered samples of crystalline 3 with a medium-pressure Hanovia mercury lamp at 0 °C for 6–12 h of irradiation occurred with remarkably high chemo- and stereoselectivity. $^1$H NMR and GC-MS analysis revealed the formation of the desired cyclopentane 2 in ca. 76% yield with no traces of the cis diastereomer after 20% conversion. Treatment of 2 with excess BBr$_3$ in CH$_2$Cl$_2$ resulted in tandem hydrolysis, ether deprotection, and lactonization to give herbertenolide (1) in 60% yield. The spectral data of the product obtained in this manner were identical to that reported for the natural product.

The exceptional simplicity, chemoselectivity, and stereospecificity of the solid-state reaction, combined with well-developed alkylation chemistry of aliphatic ketones, make it a powerful combination for the preparation of natural and nonnatural compounds containing vicinal quaternary centers. The synthesis reported in this manuscript was completed in seven steps with an overall yield of ca. 19%. Although the key step (3 → 2) was only carried out to 20–35% conversion due to subsequent melting of the methyl ester and formation of small amounts of undesirable solution phase products, higher conversions can be achieved by recycling unreacted starting material or by using lower photolysis temperatures. However, nearly quantitative solid-to-solid reactions at ambient temperatures should be possible by acylation of 7 with other alkyl cyanoformates to prepare higher melting analogues of 3. Studies involving the preparation of such compounds, the enantiospecific construction of herbertenolide, and the synthesis of other compounds in the herbertane family are currently in progress.

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Supporting Information Available: Synthetic details and characterization of compounds 1–3 and 5–7 and crystallographic data (CIF) for compound 3. This material is available free of charge via the Internet at http://pubs.acs.org. OL0499250