ORGANIC LETTERS

2006
Vol. 8, No. 6
1249−1251

Strained Polycycles by H^5C^{5x} Free-Radical Cascades†

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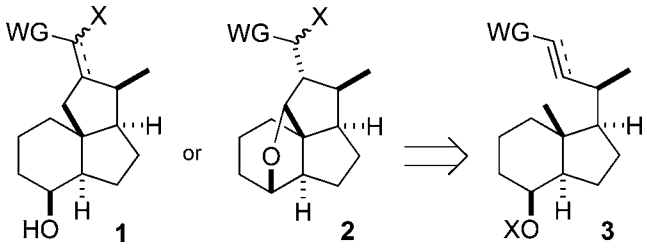
Received January 26, 2006

ABSTRACT



An H^5C^{5x}-type free-radical chain reaction selectively generates up to three new bonds and three new stereocenters in one pot. This previously unexploited strategy provides a straightforward route to the tricyclic cyclopenta[*c*]indene skeleton, present in a wide range of pharmacologically active natural products, and can significantly simplify the synthesis of other strained polycyclic structures by sidestepping protection, deprotection, and functional group interconversion steps.

Remarkable examples of complex asymmetric structures accessed by radical chain reactions have been reported in the last two decades,[1,2] and free-radical processes are increasingly considered as late-stage strategies in total syntheses. More particularly, the activation of C−H bonds via intramolecular hydrogen abstraction by alkoxy radicals has found important synthetic applications in the formation of the tetrahydrofuran core and in the functionalization of numerous natural products with oxygen, nitrogen, halogen, and sulfur.[3−6]

In the course of our work, in the synthesis of strained polycyclic vitamin D analogues, it occurred to us that the in situ formation of new carbocycles at nonactivated carbons would considerably simplify the preparation of such compounds by reducing the number of functional group interconversion steps. To our surprise, we found that the intramolecular addition of free radicals generated in situ at nonactivated carbons[7] to olefins has scarcely been investigated. Indeed, what appears to have been the only systematic study of such processes was reported by Čeković in a brief communication[8] on the photolysis of nitrites and hypochlorites derived from 8-nonenol and 9-decenol. We, therefore, decided to explore the synthetic scope of this reaction.

As a start, we decided to test the hypothesis that **1** might be accessible from **3** (Scheme 1) through a one-pot process involving the formation of an alkoxy radical at C8[9] followed

† Dedicated to Professors J. Castells and J. Elguero.

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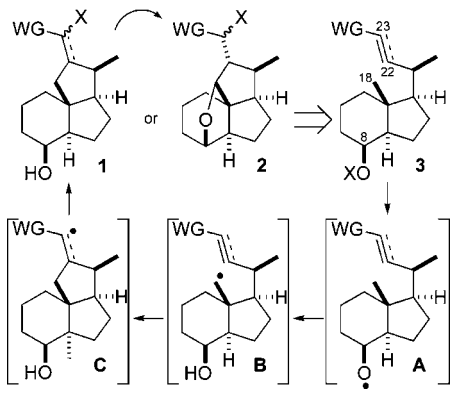
10.1021/ol060231w CCC: $33.50
Published on Web 02/21/2006

Scheme 1. Proposed Mechanism of the H^5C^{5x} Radical Cascade[a]

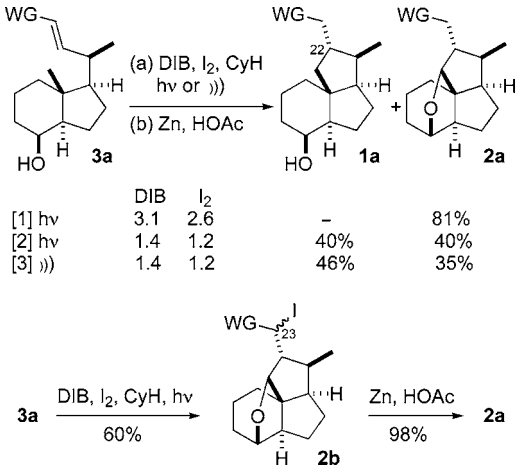


[a] WG = electron-withdrawing group (CO_2Et, CN, SO_2Ph). X = H, I, 4-nitrophenylsulfenyl.

by an H^5C^{5x} radical cascade[10] consisting of abstraction of a C18 hydrogen and intramolecular addition of the resulting radical to an electron-deficient double or triple bond.[11] To this end, Michael acceptors **3** were prepared from vitamin D_2, which required three steps and no protecting groups (see Supporting Information).

Irradiation of alcohol **3a** with a 300 W tungsten lamp under Suárez's[12] hypoiodite[13] conditions afforded unstable diastereomeric α-iodoesters that were immediately reduced with Zn in HOAc (Scheme 2). When more than 2 equiv of

Scheme 2. Irradiation of **3a** under the Hypoiodite Conditions[a]



[a] WG = CO_2Et.

diacetoxyiodobenzene (DIB) and I_2 were employed, the cyclic ether **2a** was obtained in 81% yield (Scheme 2, entry 1), presumably because of a second radical cascade initiated from the alkyl hypoiodite derivative of **1** (Scheme 1). The use of approximately stoichiometric quantities of reagents afforded equimolecular mixtures of **2a** and the tricyclic alcohol **1a** (Scheme 2, entry 2). Ultrasound[14] was an efficient substitute for irradiation (Scheme 2, entry 3). The intermediate iodide **2b** was also isolated, as a 62:38 mixture of C23 epimers.[15] Remarkably, the hypoiodite reaction thus provides up to three new bonds and three stereogenic centers.

The stereochemistry of **1a** at C22, elucidated by NOE ^1H NMR experiments on the corresponding C8−OTBDMS derivative (see Supporting Information), is as predicted by molecular mechanics conformational analysis of **3a** and complies with that observed for 4-substituted hexenyl radicals.[16] Compound **1a** would follow by abstraction of hydrogen from the solvent by the new carbon radical **C**.

We next reasoned that using a Barton-type[4a] strategy to generate the alkoxy radical would preclude the initiation of a second radical cascade from **1** and therefore the formation of compounds of type **2** (Scheme 1). Thus, homolytic cleavage of 4-nitrophenylsulfenate[17,18] **3b** in cyclohexane at room temperature yielded the desired tricyclic alcohol **1a** and thioether **1b** along with ketone **4a**, which can be easily converted to the starting alcohol (Scheme 3, entry 1).[19] Reduction of isolated **1b** with Raney nickel provided the tricyclic alcohol **1a** in 95% yield. More conveniently, direct reduction of the reaction mixture **1a** + **1b** + **4a** under the same conditions gave a mixture of alcohol **1a** and ketone **4a** (entry 2). The use of benzene as cosolvent favored the formation of **4a** (entry 3). Irradiation of **3c** produced only thioether **1d** and ketone **4b** (entry 4), but direct reduction of the reaction mixture afforded only **1c** and **4b** (entry 5). Irradiation of **3d** followed by reduction of the reaction mixture yielded sulfone **1e** (entry 6), which can be further manipulated by α-carbanion chemistry.

Irradiation of **3e**,[20] in which the unsaturation is a triple bond, produced the expected mixture of (*E*)- and (*Z*)-α,*β*-unsaturated esters **1g** along with ketone **4d** (Scheme 4). The

(9) To facilitate structural comparison, IUPAC−IUB steroid numbering is used: (a) *Pure Appl. Chem.* **1989**, *61*, 1783−1822. (b) *Eur. J. Biochem.* **1989**, *186*, 429−458. (c) *Eur. J. Biochem.* **1993**, *213*, 2.

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(15) Typical procedure for the hypoiodite-type reaction: **2a**; DIB (0.36 g, 1.12 mmol) and I_2 (0.24 g, 0.95 mmol) were added to deoxygenated 9:1 cyclohexane/benzene (50 mL). A solution of ester **3a** (0.1 g, 0.36 mmol) in CyH (5 mL) was added. The reaction mixture was irradiated with a 500 W lamp for 130 min and concentrated to dryness. Zn powder (1.6 g, 24.47 mmol) was added to a solution of the residue in HOAc (30 mL), and this mixture was stirred for 16 h.

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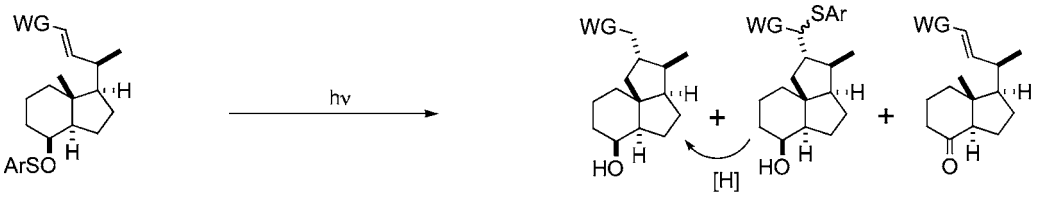
(19) Refluxing in toluene also promotes the reaction (data not shown).

(20) Typical procedure for the Barton-type reaction: **1a**; a solution of sulfenate **3b** (0.200 g, 0.46 mmol) in CyH (60 mL) was irradiated with a 300 W tungsten lamp for 60 min. After concentration, nickel Raney W-2 (0.5 g, 8.5 mmol, Fluka) was added to a solution of the residue (0.2 g) in anhydrous ethyl alcohol (20 mL), and this mixture was refluxed for 1 h.

Scheme 3. Irradiation of *p*-Nitrophenylsulfenates **3b**−**d**[a]

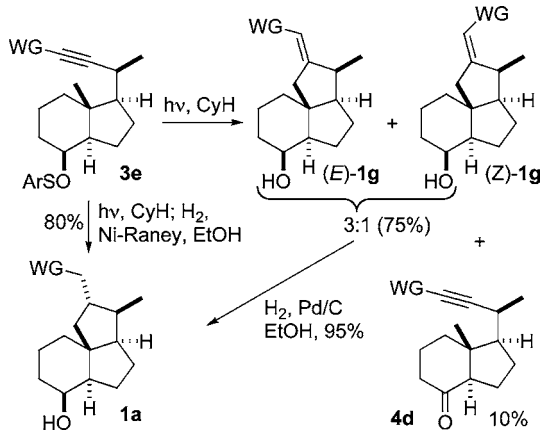


		hν	[H] (%)			
[1]	**3b**, WG=CO_2Et	CyH	Ni-Raney, EtOH, Δ, (95)	**1a**, 50%	**1b**, 21%	**4a**, 24%
[2]	**3b**, WG=CO_2Et	CyH	Ni-Raney,EtOH, Δ	**1a**, 70%	**1b**, ---	**4a**, 24%
[3]	**3b**, WG=CO_2Et	CyH/PhH(3:1)	----	**1a**, 31%	**1b**, 34%	**4a**, 34%
[4]	**3c**, WG=CN	CyH/PhH(3:1)	Ni-Raney, EtOH, Δ, (95)	**1c**, ---	**1d**, 65%	**4b**, 28%
[5]	**3c**, WG=CN	CyH/PhH(3:1)	Ni-Raney, EtOH, Δ, (95)	**1c**, 50%	**1d**, ---	**4b**, 40%
[6]	**3d**, WG=SO_2Ph	CyH/PhH(3:1)	NiB_2, EtOH, Δ, (80)	**1e**, 50%	**1f**, ---	**4c**, 43%

[a] ArS = 4-nitrophenylsulfenyl.

configuration of the C22 double bond in (*Z*)-**1g** and (*E*)-**1g** was established by 1D DPFGSE-NOESY analysis of the pure isomers (see Supporting Information). No cross-coupled thioether products were observed, presumably because the vinylic radicals **C** (Scheme 1) capture a hydrogen radical from the solvent. Hydrogenation of the mixture (*Z*/*E*)-**1g** to alcohol **1a** was achieved with a variety of catalysts. Remarkably, irradiation of **3e** followed by hydrogenation of the reaction products provided alcohol **1a** in 80% yield.

Scheme 4. Irradiation of **3e**[a]



[a] WG = CO_2Et.

In conclusion, these results show that the H^5C^{5x}-type radical cascade is a predictable and synthetically useful process. In this work, it provided a straightforward route to the tricyclic cyclopenta[*c*]indene skeleton,[21] which is present in a wide range of pharmacologically active natural products as well as in a novel family of vitamin D_3 analogues.[22]

Acknowledgment. This work was supported by the Spanish DIGICYT (Projects SAF-2001-3187 and SAF-2004-1885). We thank Solvay Pharmaceuticals BV (Weesp, The Netherlands) for the gift of vitamin D_2. D.N. thanks the Argentinian National Council for Scientific Research (CONICET) for a postdoctoral fellowship.

Supporting Information Available: Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060231W

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