The Tandem Bergman-Radical Cyclization: A New Method For Ring Annulation

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Abstract: Heating of enediynes 1a, 1b and 2 at 210° C in a sealed tube in the presence of a hydrogen atom source yields naphthalene derivatives 3a, 3b and 4 in yields of 53-72%.

In recent years, the emergence of enediyne antitumor antibiotics such as calicheamicin, esperamicin, and dynemicin A has sparked renewed interest in the Bergman cyclization reported in the early 1970's.¹ While the majority of the research in this area has been focused towards the synthesis of enediyne natural products² and their synthetic analogs,³ we are aware of no examples in which the Bergman diyl has been used as a precursor for radical cyclizations.⁴ We have completed model studies employing a Bergman cyclization followed by a radical cyclization of one of the resultant diyl radicals into an sp² carbon either five or six centers away. Reported within is the first radical cyclization of a Bergman generated aromatic 1,4-diyl with an α , β unsaturated ester to yield either a [6.6.5] or [6.6.6] angular ring system.





When compound **1a** was heated to 210° C in chlorobenzene in the presence of 1,4-cyclohexadiene (hydrogen atom donor), the 3,4-dihydrobenz-[*e*]-indene **3a** was isolated in 72% yield (Scheme 1).^{5a,6} When compound **2** (R= H, n= 2) was subjected to the same reaction conditions, two products **4** and **5** were formed in 53% and 42% yields respectively.^{5c,d} The formation of product **5** was not surprising since in general 6-exo cyclizations are slower than 5-exo cyclizations.⁷

Attempts to shift the product distribution toward the tricyclic product 4 by employing low concentrations of hydrogen atom donor had no effect on the product ratio. In order to rule out the presence of a second hydrogen atom donor in the reaction, the reaction was run in the absence of 1,4-cyclohexadiene resulting in no formation of product. This result suggests the rate constants for the radical cyclization of the Bergman diyl intermediate and the rate of hydrogen trapping of the diyl may be of the same order of magnitude. Another possibility is that the less stable aromatic radical undergoes a 1,5 hydrogen atom abstraction of the γ -position of the α , β unsaturated ester leading to the more stable allyl radical which then undergoes hydrogen atom trapping.⁸ Studies are in progress to determine which of these mechanisms are operating.

To test whether the Bergman-radical cyclization will tolerate two internal acetylenes, we extended this methodology to substrate **1b**. This compound was heated to 210° C for 24 hours and product $3b^{5b}$ was obtained in 58 % isolated yield. In all three examples, mass balance in the reaction could be accounted for by polymeric material formed in the reaction which was isolated but not characterized.

Compounds **1a,b** and **2** are easily accessed in four or five high-yielding steps.^{9,10} The synthesis of **1a** is shown below (Scheme 2).





Scheme 2: a) PDC (1.5 eq), Celite (86 %), CH_2Cl_2 ; b) trimethylphosphonoacetate (1.4 eq), DBU (1.4 eq), LiCl (2 eq), CH_3CN (89 %); c) diiodobenzene (1 eq), bis-ditriphenylphosphine palladium chloride (0.05 eq), NEt₃ (3 eq), CuI (0.1 eq) THF (94 %); d) TMS acetylene, same as c; e) MeOH, K_2CO_3 (cat.) (97 % from 8).

Absolute structural determination of 3a was achieved in a five step alternate synthesis (Scheme 3).11



Scheme 3: a) NBS (0.95 eq), benzoyl peroxide (0.05 cat.), CCl₄ (60%); b) allyl magnesium chloride (2 eq), Et₂O (89%); c) O₃, 5% MeOH in CH₂Cl₂ (73%); d) trimethyl-phosphonoacetate (1.4 eq), DBU (1.4 eq), LiCl (2 eq), CH₃CN (68%); e) n-Bu₃SnH (1.65 eq), AIBN (cat.), toluene (25%)

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After evaluating the ¹H NMR data for compound **3a**, the resonance of the C₄ methylene proton at 4.12-4.17 ppm was puzzling.^{5a} This proton resonance might be expected to come between 2 and 3 ppm. This unusual chemical shift can be explained by conformational preferences of product **3a**. The ester carbonyl apparently prefers to lie underneath and parallel to the naphthalene ring to avoid electron-electron interactions between the π cloud of the aromatic ring and the ester carbonyl. In this conformation, the carbonyl deshielding region points directly at one of the C₄ methylene protons shifting this proton resonance uncharacteristically downfield.

In conclusion, a new method for ring annulation has been developed by using the Bergman cyclization diyl as a radical precursor for further radical cyclizations into α , β unsaturated esters. It has been shown that either the 5-exo or 6-exo products can be formed and that the cyclization will occur with sterically demanding functionality in the second acetylenic position. Other variations of this ring annulation procedure including bis-radical cyclizations are under study in our laboratory and will be presented in due course.

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- 5. (a) 3a Rf= 0.48 in hexane / ethyl acetate (3 : 1). IR (neat) v 3053, 2948, 1734, 1435, 1166 cm⁻¹; ¹H NMR (CDCl₃, 300 mHz) 7.89 (d, 1H, J= 8.3 Hz), 7.85 (d, 1H, J= 8.3 Hz), 7.69 (d, 1H, J= 8.3 Hz), 7.36-7.52 (m, 3H), 4.12-4.17 (m, 1H), 3.72 (s, 3H), 3.18 (dd, 1H, J= 15.3, 9 Hz), 2.99 (dd, 1H, J= 15.3, 9 Hz), 2.80 (dd, 1H, J= 15.3, 3.3 Hz), 2.33-2.43 (m, 2H), 2.10 (dd, 1H, J= 13.3, 7.7 Hz); ¹³C NMR 173.3, 140.7, 140.6, 132.8, 129.5, 128.7, 127.7, 126.2, 124.7, 123.5, 123.3, 51.7, 40.4, 38.6,

31.5, 31.0; HRMS-EI m/z calcd for C₁₆H₁₆O₂ (M⁺) 240.1150, found 240.1153; (b) 3b Rf= 0.55 in hexanes / ethyl acetate. IR (neat) v 3062, 2952, 1740, 1079 cm⁻¹; ¹H NMR (CDCl₃) 7.79-7.86 (m, 2H), 7.71 (s, 1H), 7.37-7.48 (m, 2H), 4.81 (s, 2H), 4.14 (m, 1H), 3.72 (s, 3H), 2.93-3.09 (m, 2H), 2.48 (dd, 2H, J= 15.4, 11.1 & 3.0 Hz), 2.06-2.16 (m, 2H), 0.96 (s, 9H), 0.117-0.125 (s, 6H); 13 C NMR 173.3. 140.9, 138.6, 135.7, 133.2, 128.0, 127.5, 125.7, 124.8, 124.3, 123.4, 63.5, 51.7, 40.2, 38.7, 30.9, 29.7, 29.3, 26.0, 18.5, -5.2; HRMS-EI m/z calcd for C23H32O3Si (M⁺) 384.2121, found 384.2107; (c) 4 Rf= 0.5 in hexanes / ethyl acetate (3 : 1); IR (neat) 3050, 2931, 1734, 1167 cm⁻¹; ¹H NMR (CDCl₃) 8.39 (dd, 1H, J= 8.3, 1.3 Hz), 7.78 (dd, 1H, J= 8.3, 1.3 Hz), 7.61 (d, 1H, J= 8.3 Hz), 7.51 (ddd, 1H, J= 7.8, 6.9, 1.3 Hz), 7.40 (ddd, 1H, J= 7.8, 6.9, 1.3), 7.16 (d, 1H, J= 8.3 Hz), 4.05 (m, 1H), 3.76 (s, 3H), 2.92 (m, 1H), 2.80 (dd, 1H, J= 15.3, 2.6 Hz), 2.60 (dd, 1H, J= 15.3, 11.4 Hz), 1.89-1.97 (m, 5H); ¹³C NMR 173.3, 134.1, 133.6, 132.5, 131.4, 128.8, 128.1, 126.7, 126.3, 124.7, 122.6, 51.7, 39.7, 30.6, 30.0, 26.7, 17.6; HRMS-EI m/z calcd C17H18O2 (M⁺) 254.1307, found 254.1295; (d) 5 Rf= 0.48 in hexane / ethyl acetate (3 : 1); IR (neat)v 3050, 2918, 1718, 1028 cm⁻¹; ¹H NMR (CDCl₃) 7.77 (m, 3H), 7.59 (s, 1H), 7.42 (m, 2H), 7.30 (m, 1H), 6.99 (dt, 1H, J= 15.6, 6.9 Hz), 5.83 (d, 1H, J= 15.6 Hz), 3.72 (s, 3H), 2.79 (t, 2H, J= 7.5 Hz), 2.26 (q, 2H, J= 7.4 Hz), 1.86 (p, 2H, J= 7.4 Hz); 13 C NMR 140.0, 127.9, 127.6, 127.4, 127.1, 126.6, 125.9, 125.8, 125.2, 125.1, 122.3, 121.3, 51.5, 35.4, 31.6, 29.6, the carbonyl carbon was not detected; HRMS-EI m/z calcd for C17H18O2 (M⁺) 254.1307, found 254.1296.

- 6. General procedure for cyclization: To a predried high pressure reaction vial was added 1.8 mL chlorobenzene, and 1a (39.9 mg, 0.17 mmol). The reaction vial was degassed by a series of four freeze-pump-thaw cycles, then 1,4-cyclohexadiene (0.4 mL, 4.2 mmol) was added via syringe. The reaction vial was sealed under nitrogen and placed in an oven for 19 hours at 210° C. (The reaction vial used in the cyclization reactions consisted of a #11 screw top joint purchased from Ace glass which had been sealed on the bottom by a glassblower and had been fitted with a #11 Teflon screw cap). Isolation of the 3,4-dihydro-2-methylacetatebenz-[e]-indene derivative was achieved by silica gel column chromatography of the reaction mixture with hexanes / ethyl acetate (95 : 5). Rf= 0.48 in hexanes / ethyl acetate (3 : 1). Yield (30.1 mg, 72%)
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