Terminator Regulated Mechanistic Divergence in BF_3·$MeNO_2$ Promoted Cascade Annulations of Geometrically Defined Trienoate Derivatives

Scott R. Harring and Tom Livinghouse*†

Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT 59717, USA

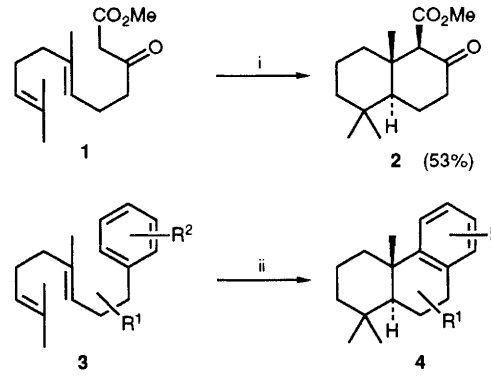
The outcome of BF_3·$MeNO_2$ promoted cascade cyclizations involving several di- and tri-enoates is shown to be strongly coupled to the nature of the terminating moiety.

Cationic cyclizations of di- and tri-enoate derivatives initiated by phenylselenenium[1–4] and phenylsulfenium[3] cation equivalents have proven quite useful for the preparation of key synthetic intermediates. White has noted that the direct, nonsulfenylative cyclization of dienoate **1** to the bicyclic product **2** can be accomplished in modest (53%) yield in the presence of 5 equiv. of $SnCl_4$ at 25 °C.[5] We have discovered that gaseous BF_3 dissolved in $MeNO_2$ is an *unusually* effective catalyst for effecting cationic cascade annulations leading to structurally diverse octahydrophenanthrene derivatives (Scheme 1).[6]

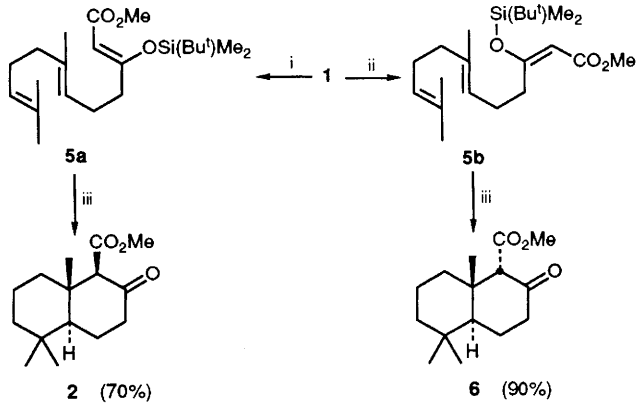
In this communication we describe an unexpected tricyclization of **1** as well as the concordant cyclization modes of its enol derivatives when BF_3·$MeNO_2$ is utilized at the cationic initiator. The (*Z*)- and (*E*)-β-silyloxyenoates **5a** and **b** were readily prepared by the silylation of β-ketoester **1** under aprotic (Bu^tMe_2SiOTf–NaH)[7] or protic (Bu^tMe_2SiCl–imidazole) conditions, respectively.‡ Cyclization of the (*Z*)-isomer **5a** in the presence of gaseous BF_3 (4.2 equiv.) dissolved in $MeNO_2$ (−20 °C, 3 h) provided **2** (Scheme 2) as the exclusive cyclized product in 70% recrystallized yield (m.p. 85–86 °C; lit.[5] 85.5–87 °C). Exposure of **5b** to 4.2 equiv. of BF_3 in $MeNO_2$ (−20 °C, 3 h) led to the exclusive formation of the *axial* β-ketoester **6** (Scheme 2) in 90% recrystallized yield

† Fellow of the Alfred P. Sloan Foundation 1989–1991.

‡ All new compounds were fully characterized by spectroscopic (^1H and ^{13}C NMR, IR) techniques and possessed satisfactory high resolution mass assignments or combustion (C, H) analyses.

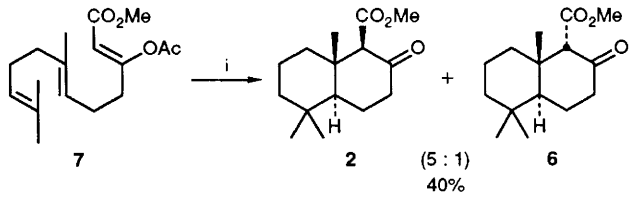


Scheme 1 *Reagents and conditions*: i, $SnCl_4$, 25 °C; ii, BF_3·$MeNO_2$, −20 °C

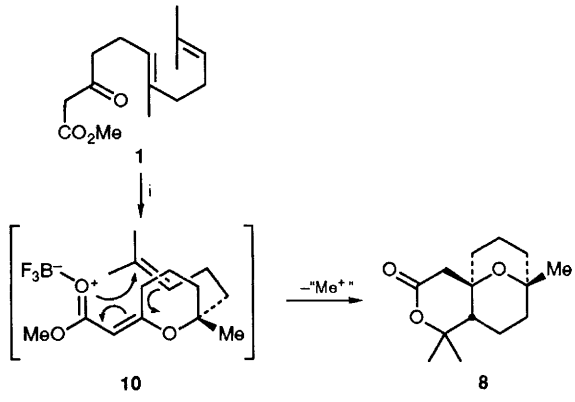


Scheme 2 *Reagents and conditions*: i, NaH, Bu^tMe_2SiOTf; ii, Bu^tMe_2SiCl, imidazole; iii, BF_3–$MeNO_2$, −20 °C

(m.p. 105–106 °C).§ The relative stereochemistry indicated for **6** was supported both by ^1H NMR spectroscopy§ and single crystal X-ray diffraction experiments. Moreover, exposure of **6** to a catalytic quantity of DABCO (1,4-diazabicyclo-[2.2.2]octane) in C_6D_6 led to rapid conversion to the equatorial isomer **2** as established by ^1H NMR spectroscopy. The near quantitative cyclization of **5b** to **6** in the presence of BF_3·$MeNO_2$ is noteworthy. Polyene substrates bearing (*E*)-disposed terminators typically undergo cyclization less efficiently than the corresponding (*Z*) isomers when conventional methods for effecting annulation are employed.[8] By way of contrast, cyclization of the (*Z*)-enol acetate **7** [BF_3 (4.2 equiv.)–$MeNO_2$, −20 °C, 12 h] occurred less efficiently to provide **2** along with **6**, (Scheme 3) **2**:**6** = 5 in 40% chromatographed yield.



Scheme 3 *Reagents and conditions*: i, BF_3–$MeNO_2$, −20 °C



Scheme 4 *Reagents and conditions*: i, BF_3–$MeNO_2$, −20 °C

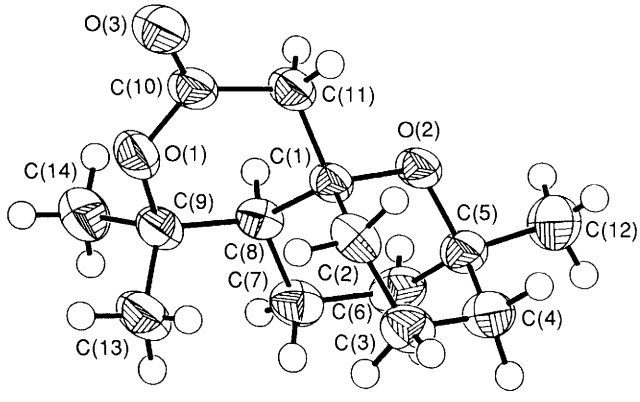


Fig. 1

The BF_3·$MeNO_2$ catalysed cyclization of the parent β-ketoester **1** took a completely different (and quite unexpected) course. Accordingly, exposure of **1** to BF_3 (4.2 equiv.) in $MeNO_2$ (−20 °C, 1 h) provided the interesting tricyclic lactone **8** in 84% recrystallized yield (m.p. 122–124 °C). Support for the structure assigned to **8** was provided by a single crystal X-ray diffraction experiment. The results of this study are depicted in Fig. 1, structure **9**. Presumably **8** arises by initiation of cyclization at the internal (*E*)-alkene of **1** with concomitant interception by the β-carbonyl oxygen to generate **10** (Scheme 4). Subsequent cyclization of **10** either by an inverse electron demand [4 + 2] cycloaddition or a stepwise cationic process involving the peripheral alkene followed by *O*-demethylation would then provide **8**, Scheme 4.

In summary, cationic cascade cyclizations of relatively simple trienoates and related compounds promoted by

§ A representative experimental procedure is as follows: for 1-methoxycarbonyl-2-oxo-1β,2,3,4,4aα,5,6,7,8,8aβ-octahydro-5,5,8a-trimethylnaphthalene **6** a flame dried 25 × 150 mm test tube equipped with a magnetic stirring bar, rubber septum, and N_2 inlet was flushed with N_2 then charged with $MeNO_2$ (5.0 ml), and cooled to −20 °C. BF_3·$MeNO_2$ [(1.044 mol dm^{-3} in $MeNO_2$) 1.42 ml, 1.48 mmol], was added in one portion *via* syringe and the resulting solution was stirred for 15 min at −20 °C. A solution of the (*E*)-silyl enol ether **5b** (0.129 g, 0.35 mmol) in $MeNO_2$ (1.0 ml) was then added in one portion *via* syringe and the resulting mixture was stirred for 1 h at −20 °C. The reaction was quenched (at −20 °C) with saturated $NaHCO_3$ (5 ml) and the mixture was allowed to warm to room temperature. The layers were separated and the organic phase was washed with H_2O (2 × 5 ml). The combined aqueous layers were back extracted with CH_2Cl_2 (3 × 5 ml) and the combined organic phase was dried with $MgSO_4$. The solvents were evaporated to furnish the crude product which was recrystallized from light petroleum (b.p. 30–60 °C) to afford 0.794 g (90%) of **6** as a single diastereoisomer. For **6**: ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H, OMe), 2.90 (d, *J* 1.5 Hz, 1H, CH), 2.89 [m, *J* 7.4 Hz, 1H, C(O)H–H'], 2.37 [dm, *J* 2.3, 14.6 Hz, 1H, C(O)H'–H], 2.11 (dd, *J* 3.2, 12.8 Hz, 1H, CH ring junction), 1.96 [m, 1H, C(22)–H'], 1.63–1.34 [cm, 5H, C(18) H_2, C(22)–H, C(41)–H', C(37)–H], 1.25 [dd, *J* 3.7, 13.3 Hz, 1H, C(37)–H], 1.16 [dd, *J* 3.7, 13.1 Hz, 1H, C(41)–H], 0.94 (s, 3H, Me), 0.91 (s, 3H, Me), 0.81 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 206.89 (C=O ketone), 169.25 (C=O ester), 70.69 (CH), 51.68 (OMe), 43.99 (CH), 41.59 (CH_2), 39.75 (CH_2), 37.92 (CH_2), 33.11 (Me), 22.65 (CH_2), 21.90 (Me), 20.84 (Me), 18.49 (CH_2); IR (KBr, ν/cm^{-1}) 3006–2852 (CH envelope), 1726 (C=O), 1708 (C=O), 1424, 1190, 1156 and 1004; high resolution mass spectrum calc. for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1722.

BF_3·$MeNO_2$ represent efficient and complementary alternatives to annulations performed using conventional modes of catalysis.

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