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Total synthesis of (±)-dihydroactinidiolide using selenium-stabilized carbenium ion

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This article is dedicated to Professor R. C. Boscaini (in memoriam) by their valuable contributions on the organic synthetic chemistry field

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ABSTRACT

A new, short total synthesis of dihydroactinidiolide **1** is described using selenium carbenium ion-promoted carbon–carbon bond formation as the key step. Our synthetic strategy starts with a lactonization reaction between 1,3,3-trimethylcyclohexene **13** and α-chloro-α-phenylseleno ethyl acetate **14**, affording the key intermediate, α-phenylseleno-γ-butyro lactone **15**, which reacted via a selenoxide elimination to the target compound **1**.

Dihydroactinidiolide **1** was first isolated as felines attractant from leaves of *Actinidia polygama*[1] and has been identified as a flavour component in many plants such as tobacco[2] and tea.[3] The closely related compounds dihydroactinidiolide **1**, tetrahydroactinidiolide **2**, isodihydroactinidiolide **3**, actinidiolide **4**, loliolide **5** and epiloliolide **6** have been studied as germination inhibitors in wheat grains (Fig. 1).[4]

Dihydroactinidiolide **1** is one of three components of the pheromone for queen recognition of the workers of the red imported fire ant (RIFA), *Solenopsis invicta*.[5] Since its introduction in the early 1930s, RIFA has become a major agricultural and urban pest throughout the southeastern USA. In addition, fire ants cause both medical and environmental harm.[6]

Due to its economic significance, different racemic[7] and enantioselective[8] syntheses of dihydroactinidiolide **1** have been reported; the most classical one is that described by Mori and Nakazono.[7b]

Organoselenium compounds have been known for a long time as versatile reagents in organic chemistry, and in recent years there has been considerable development of selenium-based methods in organic synthesis.[9] Among the several transformations using organoselenium reagents, the selenium carbenium ion-mediated carbon–carbon bond formation has emerged as a useful protocol for preparation of complex molecules,[10–12] as recently demonstrated in the preparation of naturally occurring heritonin.[11a]

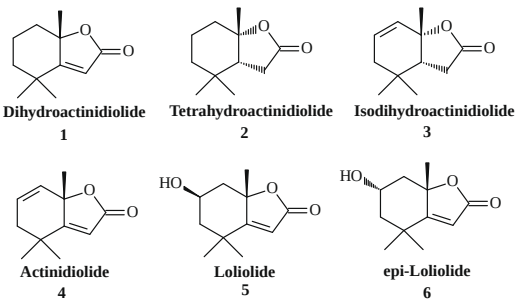

Figure 1. Dihydroactinidiolide (**1**) and related compounds.

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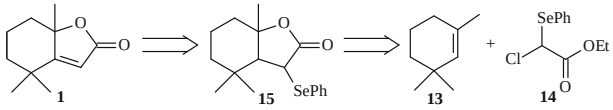
Versatile reagents to explore the ability of selenium to stabilize adjacent carbocations are α-halo-α-phenylseleno esters, first described by our group for the preparation of anti-inflammatory aryl acetic acids via a Friedel–Crafts reaction.[11b] This useful reagent[11c] was used also in the reaction with silyl enol ethers, in the presence of $ZnBr_2$ as Lewis acid, giving α-phenylseleno-γ-keto esters in good yields.[11d] When terminal and internal alkenes were used as a nucleophile in the presence of $SnCl_4$, α-phenylseleno-γ,δ-unsaturated esters and α-phenylseleno-γ-butyro lactones were synthesized, respectively, in an 'ene type' reaction.[12]

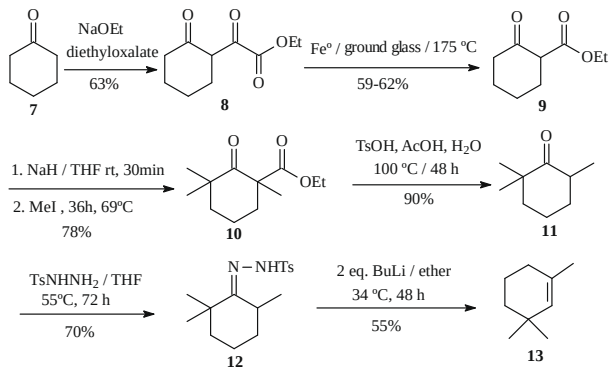
Because of our interest in the synthesis and reactivity of organoselenium compounds, we describe here our results on the total synthesis of dihydroactinidiolide **1** using selenium carbenium ion-promoted carbon–carbon bond formation as the key step. Our synthetic strategy is depicted in Scheme 1, and starts with an ene-reaction between α-chloro-α-phenylseleno ethyl acetate **14** and 1,3,3-trimethylcyclohexene **13**, affording the key intermediate, α-phenylseleno-γ-butyro lactone **15**, which undergoes a selenoxide elimination to the target compound **1** (Scheme 1).



Scheme 1.

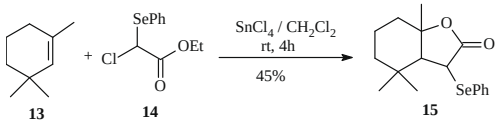
Our initial efforts were made with the aim of preparing the starting alkene **13**. After many unsuccessful attempts using isophorone as the starting material, the alkene 1,3,3-trimethylcyclohexene **13** was prepared from cyclohexanone.[13–21]

The reaction of cyclohexanone **7** with diethyloxalate in the presence of sodium ethoxide gave the intermediate **8** in 63% yield after purification by distillation. Then, the product **8** was immediately submitted to pyrolysis by treatment with a catalytic mixture of ground iron and ground glass at 175 °C, giving the carboethoxy cyclohexanone **9** in 59–62% yield from cyclohexanone.[13] Next, the carboethoxy cyclohexanone **9** was treated with excess of NaH and MeI, respectively, under reflux for 4 h and then at room temperature for 36 h, to give 6-carboethoxy-2,2,6-trimethylcyclohexanone **10** in 78% yield.[15] Elimination reaction of **10** with *p*-toluenesulfonic acid in acetic acid and H_2O at rt for 48 h gave 2,2,6-trimethylcyclohexanone **11** in 90% yield.[15] The reaction of ketone **11** with *p*-toluenesulfonylhydrazine gave tosylhydrazone **12** in 70% yield.[17,19] The Shapiro reaction between tosylhydrazone **12** and 2 equiv of BuLi in ether under reflux for 24 h produced the 1,3,3-trimethylcyclohexene **13** in 55% yield (Scheme 2).[17,19]



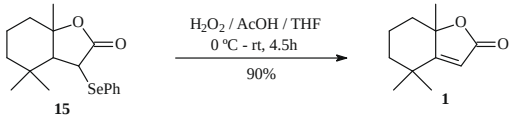
Scheme 2.

The lactonization reaction between 1,3,3-trimethylcyclohexene **13** and ethyl α-chloro-α-phenylseleno acetate **14** using $SnCl_4$ as Lewis acid and CH_2Cl_2 as solvent at room temperature, afforded the lactone **15** in 45% yield after 4 h (Scheme 3).[23]



Scheme 3.

In contrast to what was observed when other internal alkenes were used,[12] the formation of non-cyclized, α-phenylseleno-γ,δ-unsaturated esters was not detected in this reaction. Finally, the reaction between the α-phenylseleno-γ-butyro lactone **15** and 30% (v/v) H_2O_2 gave, via *syn*-elimination of the selenoxide intermediate,[7g,24] the dihydroactinidiolide **1** in 90% yield (Scheme 4).[25]



Scheme 4.

In conclusion, dihydroactinidiolide **1** was prepared directly from **13** and **14** by a lactonization-selenoxide *syn*-elimination sequence, in an overall yield of 45%. This protocol demonstrated the applicability of selenium-stabilized carbenium ions in the synthesis of naturally occurring products.

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14. Spectral data of compound **9**: GC–MS *m/z* 171(M+1), 170, 142, 124, 96, 68 (100%), 55, 41; IR (KBr, cm^{-1}): 2963, 2937, 2858, 1743, 1717, 1650, 1617, 1440, 1395, 1373, 1304, 1179, 1081, 1060, 912, 807; ^{1}H NMR (80 MHz, δ in CCl_4): 12.21 (s, 1H); 4.20 (q, *J* = 7 Hz, 2H); 3.35 (t, *J* = 8 Hz, 1H); 2.1–2.55 (m, 4H); 1.55–1.95 (m, 4H), 1.30 (t, *J* = 8 Hz, 3H). ^{13}C NMR (20 MHz, δ in CCl4): 205.82, 172.81, 172.61, 169.99, 97.78, 61.00, 60.13, 57.31, 41.85, 30.10, 29.23, 27.26, 23.43, 22.61, 22.1, 22.16, 14.36, 14.23.
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16. Spectral data of compound **10**: GC–MS *m/z* 213(M+1), 212, 184, 167, 139, 115 (100%), 102, 87, 69, 55; IR (KBr, cm^{-1}): 3399, 2977, 2935, 1735, 1707, 1462, 1299, 1244, 1207, 1177, 1151, 1120, 1080, 1028, 997, 974, 939, 855, 825, 771, 720, 661. ^{1}H NMR (80 MHz, δ in CCl_4): 4.15 (q, *J* = 7 Hz, 2H); 2.60 (s, 1H), 2.44 (s, 1H); 1.45–1.80 (m, 4H); 1.29 (s, 3H); 1.23 (t, 3H), 1.08 (s, 6H). ^{13}C NMR (20 MHz, δ in CCl_4): 209.84, 171.82, 60.30, 54.45, 45.34, 39.97, 36.16, 26.22, 24.92, 22.86, 17.95, 13.31.
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18. Spectral data of compound **11**: GC–MS *m/z* 141(M+1), 140, 97, 82 (100%), 69, 55; IR (KBr, cm^{-1}): 3392, 2967, 2930, 2868, 1706, 1454, 1383, 1315, 1244, 1126, 1019, 992, 957, 857, 825, 736. ^{1}H NMR (80 MHz, δ in CCl_4): 2.62 (sext., *J* = 6.4 Hz, 1H), 1.40–2.20 (m, 6H), 1.2 (s, 3H), 1.0 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (20 MHz, δ in CCl_4): 216.91, 44.79, 41.52, 40.37, 36.46, 25.32, 24.95, 21.26, 14.62.
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20. Spectral data of compound **12**: GC–MS m/z 310 (M+2), 309 (M+1), 153, 138, 127, 109 (100%); IR (KBr, cm^{-1}): 3387, 3214, 2926, 1597, 1458, 1398, 1340, 1291, 1166, 1093, 1018, 987, 917, 813, 707, 685. ^{1}H NMR (80 MHz, δ in CCl_4): 7.88 (d, *J* = 8 Hz, 2H); 7.30 (d, *J* = 8 Hz, 2H); 2.62–3.06 (m, 4H); 1.23–1.75 (m, 6H); 1.10 (s, 3H); 1.08 (s, 3H), 1.00 (s, 3H). ^{13}C NMR (20 MHz, δ in CCl_4): 167.69, 143.30, 135.40, 128.92, 127.79, 39.65, 38.07, 31.07, 29.07, 28.56, 28.16, 17.59, 16.53.
21. Spectral data of compound **13**: ^{1}H NMR (80 MHz, δ in CCl_4): 5.12 (s, 1H); 1.98–1.23 (m, 9H); 0.95 (s, 6H)—spectral data in accordance with Ref. 22.
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23. Spectral data of compound **15**:[7g] GC–MS *m/z* 340 (M+2), 339 (M+1), 338, 337 (M−1), 336 (M−2), 294, 257, 203, 181, 180, 137, 95, 81 (100%), 55; IR (KBr, cm^{-1}): 3473, 2969, 2930, 2860, 2339, 1752, 1577, 1474, 1438, 1379, 1261, 1203, 1163, 1102, 1046, 946, 866, 812, 745, 693. ^{1}H NMR (80 MHz, δ in CCl_4): 7.55–7.80 (m, 2H), 7.14–7.45 (m, 3H); 3.77 (d, *J* = 10,1 Hz, 1H); 1.30–2,35 (m, 7H); 1.41 (s, 3H); 1.26 (s, 3H); 0.96 (s, 3H). ^{13}C NMR (20 MHz, δ in CCl_4): 175.21, 135.48, 129.29, 128.68, 127.62, 84.72, 47.89, 46.53, 43.69, 32.82, 32.02, 30.39, 28.36, 27.03, 21.47.
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25. Spectral data of compound **1** (±)-dihydroactinidiolide:[7a] GC–MS *m/z* 181 (M+1), 180, 167, 149, 137, 135, 121, 109, 91, 69, 55 (100%). ^{1}H NMR (80 MHz, δ in CCl_4): 5.63 (s, 1H); 1.28–2.70 (m, 6H); 1.51 (s, 3H); 1.15 (s, 3H); 1.0 (s, 3H).