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Application of the double intramolecular hetero-Michael addition (DIHMA) approach in spiroketal synthesis: total synthesis of (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]-undecane, a *Dacus oleae* olive fly pheromone

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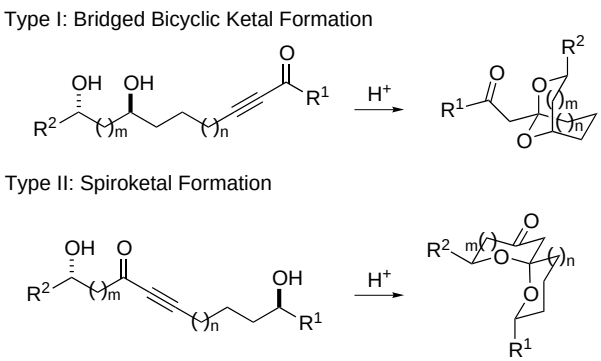
Abstract—Application of a novel double intramolecular hetero-Michael addition (DIHMA) strategy to spiroketal synthesis was illustrated by a concise synthesis of (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane, a *Dacus oleae* olive fly pheromone.

Spiroketals are significant subunits present in many natural products with biological importance, and synthesis of this type of functionality typically involves dehydrative ketalization.[1] Recently, we have developed a novel double intramolecular hetero-Michael addition (DIHMA) strategy toward the construction of the 2,9-dioxabicyclo[3.3.1]nonane system within the complex architecture of azaspiracid natural products.[2] This approach delivered the intricate bicycloketal FG rings of azaspiracid in an efficient and expedient fashion. Although the double intermolecular hetero-Michael addition has been sporadically employed in synthetic organic chemistry,[3] the potential of the hetero bis-conjugate addition, especially the intramolecular version, to assemble complex molecular frameworks has yet to be fully explored.

It was reasoned that the DIHMA strategy would be applicable to spiroketal synthesis (Scheme 1). Compared to the typical dehydrative ketalizations, the proposed synthesis of spiroketals via DIHMA has potential advantages, such as (1) the liberation of diols from their masked forms may be integrated into the bis-conjugate addition step by judicious choice of the protecting groups and deprotection conditions; and (2) the residual carbonyl functionality on the spiroketal rings would serve as a versatile synthetic handle for further manipulations. We report here the realization of the non-dehydrative DIHMA process in the synthesis of a spiroketal substructure, as demonstrated by a short total synthesis of (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane (**5**),[4] a pheromone from the rectal glands of the female olive fly (*Dacus oleae*, a major pest in the Mediterranean basin).[5]

Treatment of 5-hexyn-1-ol TBS ether (**1a**) with *n*-BuLi (Scheme 2), followed by addition of aldehyde **2** provided a propargylic alcohol (**3a**), which was oxidized to produce ynone **3** in good overall yield. Under the typical acidic conditions for the DIHMA process developed previously,[2a] cleavage of the silyl ethers was effected with CSA in MeOH and subsequent solvent exchange from MeOH to benzene promoted the bis-conjugate addition. Following the literature precedent,[6] ketone **4a** was reduced with $NaBH_4$, and acid-catalyzed



Scheme 1. Bicycloketal versus spiroketal synthesis via DIHMA.

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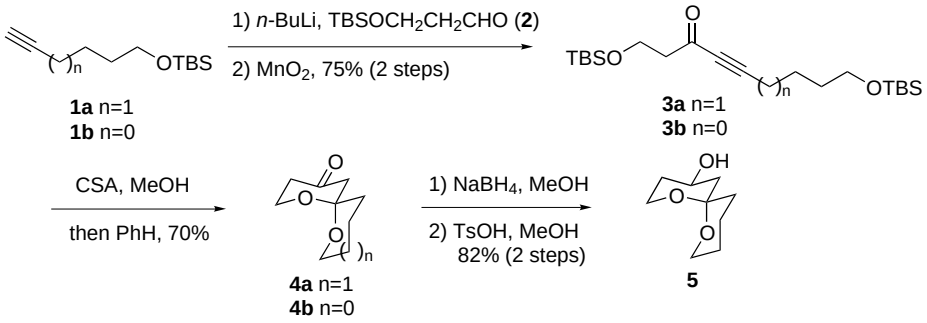

Scheme 2. Synthesis of 4-hydroxy-1,7-dioxaspiro[5.5]undecane.

isomerization provided (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane (**5**).[7] Using the same reaction sequence, 1,6-dioxaspiro[4,5]decan-9-one (**4b**)[6,8] could be prepared in comparable yields.

In summary, the total synthesis of (±)-(4*S**,6*S**)-4-hydroxy-1,7-dioxaspiro[5.5]undecane (**5**) has been completed in a convergent and concise manner that illustrates the applicability of the type II DIHMA process for accessing spiroketal motifs within natural products frameworks.

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7. Characterization data for **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.99–4.01 (m, 1H), 3.90–3.97 (m, 1H), 3.61–3.63 (m, 2H), 2.52–2.60 (m, 1H), 2.42 (broad s, 2H), 2.31–2.34 (m, 1H), 1.82–1.91 (m, 2H), 1.47–1.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.7, 99.4, 61.0, 59.0, 52.6, 41.0, 34.8, 24.4, 18.6; MS (EI) m/z 170 [M$^+$]. Characterization data for **5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07 (tt, J=5.5, 10.5 Hz, 1H), 3.53–3.73 (m, 4H), 2.00 (ddd, J=2, 5, 12.5 Hz, 1H), 1.86–1.90 (m, 1H), 1.79–1.83 (m, 1H), 1.63–1.66 (m, 1H), 1.45–1.59 (m, 5H), 1.28 (dd, J=11.5, 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 97.2, 64.3, 60.4, 58.8, 45.2, 35.5, 35.0, 25.1, 18.5; MS (EI) m/z 172 [M$^+$].
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