## Polyene Cyclization Promoted by the Cross-Conjugated $\alpha$ -Carbalkoxy Enone System. Observation on a Putative 1,5-Hydride/1,3-Alkyl Shift under Lewis **Acid Catalysis**

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Polyene cyclization of compounds 3 and 4 under catalysis with AICl<sub>3</sub> and/or SnCl<sub>4</sub> gave rise to complex bicyclic products 8 and 9, structures of which were highly unexpected, and X-ray analyses were invoked for unambiguously structural identification. Mechanistically, a tandem o-bond rearrangement process, including an unusual through-space 1,5-hydride or 1,3-alkyl shift as a key operation, is proposed.

Nature's inexhaustible ability to construct molecules of extremely high degrees of intricacy and structural complexity has been a constant fascination for synthetic organic chemists. This unique facility for bioorganic synthesis, oftentimes from the simplest building blocks, is equaled by no other. Deeply rooted in this efficient synthesis machinery is the seemingly simple paradigm of cation-promoted cyclization and bond migration processes.<sup>1–7</sup> This is highly evident in the wellaccepted biosynthetic process of a plethora of secondary metabolites.

In our quest for the establishment of efficient protocols for accessing decalin and other polycyclic systems by mirroring nature-driven cyclization processes, we discovered that  $\beta$ -keto esters 1 and 2 could undergo effective Lewis acid-catalyzed intramolecular cyclization, giving rise to decalin systems in high yields.<sup>8–11</sup> Further investigation into this interesting process led to the generation of positional analogue 3 and its homologue 4, each possessing the terminal olefin at the  $\alpha'$ -position. These compounds were individually subjected to the optimized cyclization conditions as delineated in the preceding work.8



Surprisingly, the anticipated polyene cyclization product of the individual reactions was not formed; instead, a

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molecule bearing a peculiar skeleton was obtained, the structure of which could only be ascertained unambiguously by X-ray crystallographic analysis. These structures as well as our proposed mechanistic rationalization for their formation are described herein.

Starting from 4,4-dimethylcyclohexanone, compound **3** was readily prepared via four key operations as illustrated in Scheme 1. Dimethylhydrazone **5**, formed in good yield



(85%) under standard conditions, was deprotonated with *n*-butyl lithium and alkylated with allyl bromide to give  $\alpha$ -allylic cyclohexanone **6** in 81% yield. This was followed by carbomethoxylation (**6**  $\rightarrow$  **7**) and DDQ oxidation to provide compound **3** in 63% over two steps. Enone **3** thus obtained was treated with aluminum trichloride (2 equiv) for 48 h at room temperature, giving rise to the cyclic compound **8** exclusively in 70% yield, the structure of which was determined unambiguously by an X-ray analysis. A plausible mechanistic rationale is proposed in Scheme 2.



Following the formation of an aluminoxy complex, a cascade of  $\sigma$ -bond migrations comprising 1,2-hydride, 1,3-methyl, and 1,2-methine shifts is envisioned, culminating in the formation of the bicycle[3.3.1]nonane **8**.<sup>12</sup>

Compound 4 was prepared following a similar synthetic sequence as described for compound 3 with the exception that allyl bromide was replaced with 1-butenyl bromide in the alkylation step. As in the case of compound 3, when compound 4 was treated with  $AlCl_3$  (2 equiv) or  $SnCl_4$  (2 equiv) for 2 h at room temperature, the polyene cyclization process occurred smoothly, affording product 9 in ca. 75% yield, which was identified spectroscopically and further explicated by X-ray crystallographic studies as follows.

Our proposed mechanism for the formation of **9** (Scheme 3) proceeds from the cationic intermediate upon cyclization



of the terminal olefin to the activated enone system. Again, a cascade of the  $\sigma$ -bond shift process involving 1,5-hydride, 1,2-methyl, and 1,2-methylene shifts followed by the decomposition of the metaloxy complex is proposed. The relative configuration of **9** was unambiguously confirmed by the X-ray analysis of its corresponding crystalline diol **10**,<sup>13</sup> readily provided by reduction of **9** with lithium aluminum hydride in excellent yield (92%).

Although the mechanistic rationales for the formation of these structurally novel products 8 and 9 seem reasonable (vide supra), in terms of reactions performed under standard chemical environment, the chemistry described above is unique in that one sole product is produced in rather high yield. Typically, chemical processes involving numerous bond shifts yield a multitude of products per reaction and are individually low yielding. The mechanistic rationale invoked for the generation of the resulting products may be atypical for the conditions applied but not entirely unprecedented as similar mechanistic pathways have been reported for some electron-deficient olefinic/acetylenic<sup>14</sup> and structurally highly constrained systems.<sup>15</sup> However, strictly speaking, the through-space 1,5-hydride shift proposed for the titled system is somewhat more exotic in that those described in above literatures are limited to substrates containing a  $C(sp^3)$ -H bond adjacent to a heteroatom (N, O) or an activated *tertiary* benzylic C(sp<sup>3</sup>)-H bond as a hydride donor<sup>16</sup> so that the ensuing carbocation can be stabilized by electron

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<sup>(12)</sup> CCDC 261323 (8) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc. cam.ac.uk/conts/retrieving.html or deposite@ccdc.cam.ac.uk.

<sup>(13)</sup> CCDC 261324 (10) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc. cam.ac.uk/conts/retrieving.html or deposite@ccdc.cam.ac.uk.

delocalization; this carbocation-stabilized capacity may serve, in part, as the essential driving force to facilitate the 1,5hydride shift in these systems. Nevertheless, the mechanistic pathways proposed in Schemes 2 and 3, though occurring without intermediacy of the extra stabilizing force, are considered quite normal in the living system and commonly adopted in elucidating the biosynthetic courses of the secondary metabolites, for example, trichodiene and illudins M and S, etc.<sup>17</sup>

In conclusion, we report here the observation of a highly ordered, organized, and deep-seated rearrangement process of  $\alpha,\beta$ -unsaturated cross-conjugated cyclohexenone systems as achieved under a purely chemical environment. The results indicated that the multiple  $\sigma$ -bond migration process, an enzymatic process prevalent in nature, might potentially take place under typical chemical reaction conditions and thus should not be entirely excluded nor considered aberrant in the elucidation of product formation.

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**Supporting Information Available:** Detailed experimental procedures and characterization data for all new compounds described in this paper are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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