

Polyene Cyclization Promoted by the Cross-Conjugated α -Carbalkoxy Cyclohexenone System. An Unusual 1,2-Hydride Shift under Lewis Acid Catalysis

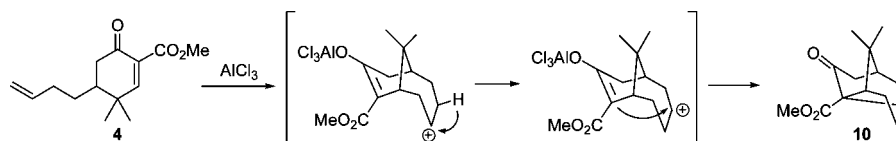
Min-Tsang Hsieh,[†] Ho-Hsuan Chou,[‡] Hsing-Jang Liu,[‡] Huang-Min Wu,[‡]
Tai Wei Ly,[§] Yen-Ku Wu,[‡] and Kak-Shan Shia^{*,†}

Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli County 350, Taiwan, R.O.C., Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30013, R.O.C., and Axikin Pharmaceuticals, Inc., 10835 Road to the Cure, Suite 250, San Diego, California 92121

ksshia@nhri.org.tw

Received December 15, 2008

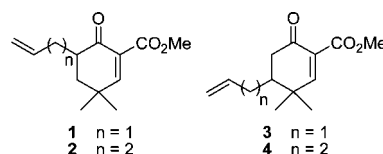
ABSTRACT



Polyene cyclization of the titled compounds under catalysis with $\text{AlCl}_3/\text{SnCl}_4$ gave rise to the corresponding polycyclic products, many of which were structurally highly unexpected, and thus, individual X-ray analysis was required to finalize the structural identification. Mechanistically, an unusual 1,2-hydride shift is proposed to elucidate the product formation.

The polyene cyclization process, commonly recognized as a highly biosynthesis-mimicking paradigm, has been widely applied to facilitate the assembly of multiple ring systems in organic synthesis. As documented, functionalities serving as effective initiators for the polyene cyclization process included epoxide,¹ acetal,² allylic alcohol,³ and α , β -unsaturated carbonyl groups (aldehyde or ketone).⁴ During the past decade, intramolecular polyene cyclization focusing on the cross conjugated α -carbalkoxy enone systems has been extensively studied in Liu's laboratories to have facile access

to various structurally complex polycyclic frameworks.⁵ Along this line, it was recently reported that enones **1** and **2** could undergo effective intramolecular cyclization under Lewis acid catalysis to give rise to structurally unusual products.^{5g} The corresponding positional analogues **3** and **4**, each possessing a terminal olefinic linker at the β' -position, were then prepared.



Compounds thus obtained were treated with an appropriate Lewis acid under standard reaction conditions to effect polyene cyclization as indicated in the preceding work.^{5g} Most of the cyclization products failed to be elucidated by

[†] National Health Research Institutes.

[‡] National Tsing Hua University.

[§] Axikin Pharmaceuticals, Inc.

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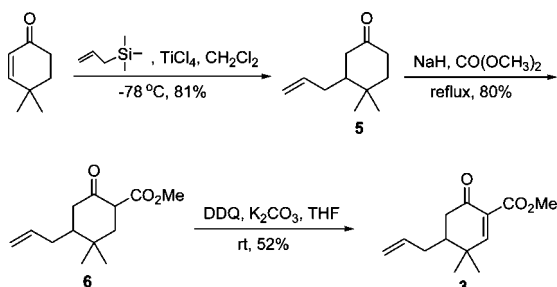
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general spectral data, and X-ray crystallographic analyses were required to finalize the structural identification. Details of this investigation will be described as follows.

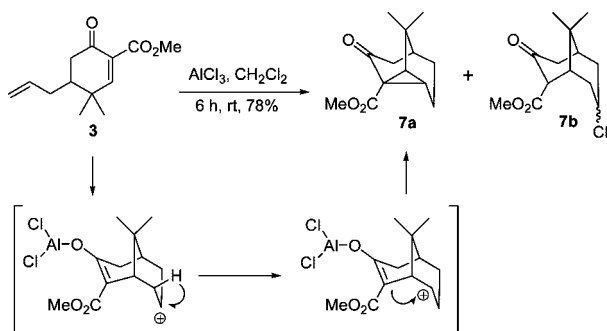
Enone ester **3** was readily prepared from commercially available 4,4-dimethyl-2-cyclohexen-1-one through a three-step sequence as illustrated in Scheme 1. Hosomi–Sakurai

Scheme 1



addition of allyltrimethylsilane to 4,4-dimethyl-2-cyclohexen-1-one in the presence of TiCl_4 at $-78\text{ }^\circ\text{C}$ afforded compound **5** in 81% yield. Subsequent treatment of **5** with dimethyl carbonate using NaH as a base gave rise to keto ester **6** (80%) as an inseparable mixture of keto and enol isomers, which in turn were oxidized by DDQ to provide the desired **3** in 52% yield. The carbomethoxylation occurred in a highly regioselective manner, which was somewhat unexpected, and thus accelerated the entire synthetic process. With enone ester **3** in hand, the intramolecular polyene cyclization was then explored. Upon treatment with aluminum trichloride (2 equiv) at ambient temperature, a separable mixture of products **7a** and **7b** was obtained in a 1.1:1 ratio in 78% yield. The structure of **7a** was determined unambiguously by X-ray analysis,⁶ and a pair of inseparable diastereomers **7b** were tentatively assigned based on the previously structurally closely related compounds.^{5a–c} A plausible mechanistic rationale is proposed in Scheme 2.

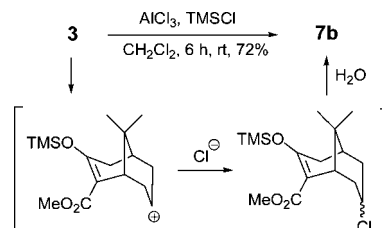
Scheme 2



Following an ensuing aluminoxo complex, we envisaged that a tandem migration process including a 1,2-hydride shift took place, resulting in the formation of the tricyclo[3.3.1.0]–

nonane **7a**. To further investigate the mechanistic aspects, compound **3** under treatment with both AlCl_3 and TMSCl (Scheme 3), an enolate-trapping agent, was also carried out

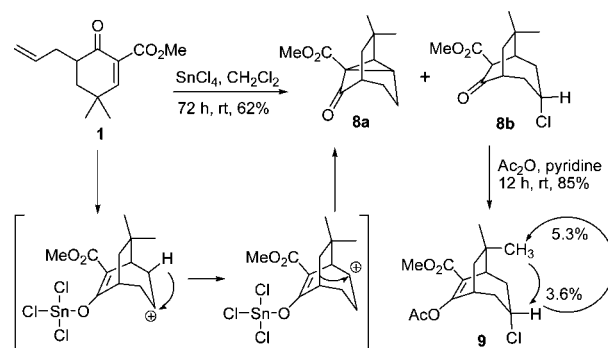
Scheme 3



at the same reaction conditions. As a result, only a ca. 1:1 mixture of epimeric chlorides **7b** was formed in 72% yield, implying that the ensuing enolate might play a critical role in promoting the 1,2-hydride shift; however, exactly what driving force triggers the proposed 1,2-hydride shift is still not fully understood and thus more evidence is required before any conclusions can be derived.⁷

Similar product outcomes were also observed with enone ester **1** upon treatment with SnCl_4 . As illustrated in Scheme 4, the resulting tricyclo[3.3.1.0]nonane **8a** and chloride **8b**

Scheme 4



were obtained in 22% and 40% yield, respectively. The structure of **8a** was unambiguously determined by an X-ray analysis.⁸ However, the stereochemistry of chloride **8b** was ascertained via its corresponding acetate **9** by NOE experi-

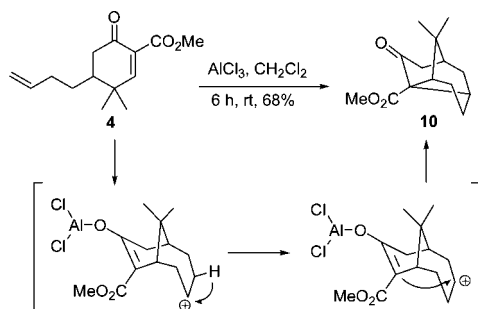
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ments.⁹ The product formation of **1** was found to be catalyst dependent as compared to the preceding work wherein compound **1** was catalyzed with AlCl_3 , affording a single product with the bicyclo[3.3.1]nonane skeleton instead.^{5g}

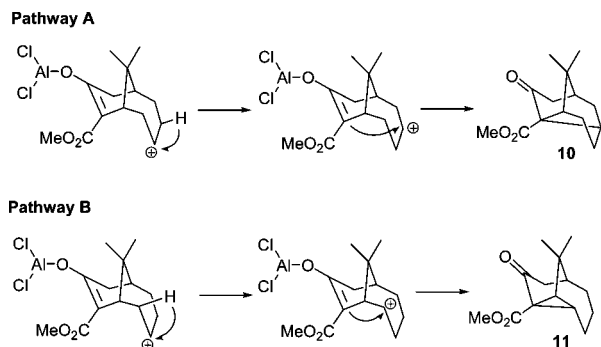
The preparation of enone ester **4** was fulfilled following a similar synthetic sequence as described for **3** with the exception that the Hosomi–Sakurai addition was replaced with a regular 1,4-conjugate addition with 3-butenylmagnesium bromide in the presence of copper(I) iodide. Similarly, when **4** was treated with AlCl_3 (2 equiv) for 6 h at ambient temperature (Scheme 5), the polyene cyclization process

Scheme 5



occurred smoothly to afford tricyclo[4.3.1.0]decane **10** exclusively in ca. 68% yield, the structure of which was characterized spectroscopically and further substantiated by X-ray crystallographic studies.¹⁰ Our proposed mechanism for the formation of **10** proceeds from the cationic intermediate upon cyclization of the terminal olefin to the activated enone unit followed by a series of tandem rearrangements involving 1,2-hydride migration and the through-space ring closure. However, as depicted in Scheme 6, what factors

Scheme 6



direct the pathway A for **10** rather than pathway B for **11**, appearing more preferred in terms of the spatial distance between α anion and the ensuing carbocation, remains unclear and is worth further studies. Indeed, the 1,2-hydride shift proposed for the above systems is somewhat unusual as compared to those described in many historical cases, where they are limited to substrates containing a $\text{C}(\text{sp}^3)\text{--H}$ bond adjacent to an oxygen atom¹¹ or a *tertiary* benzylic $\text{C}(\text{sp}^3)\text{--H}$ bond¹² as a hydride donor so that the ensuing carbocation could be stabilized by electron delocalization; this carbocation-stabilizing ability is believed to serve, in part, as the essential driving force to facilitate the 1,2-hydride shift in these systems.

In conclusion, under catalysis with an appropriate Lewis acid, the α -activated cross-conjugated cyclohexenone systems might undergo polyene cyclization in an enzyme-mimicking way to afford various carbon skeletons which are difficult to access by other existing methods. In addition, the product formation was found to be catalyst-dependent, thus making the titled systems not only useful in organic synthesis but also challenging in mechanistic aspects.

Acknowledgment. We are grateful to the National Health Research Institutes and National Science Council of the Republic of China for financial support.

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

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(6) CCDC 261323 (**7a**) 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 deposit@ccdc.cam.ac.uk.

(7) All the 1,2-hydride shifts represented in the paper are presumably reversible.

(8) CCDC 261322 (**8a**) 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 deposit@ccdc.cam.ac.uk.

(9) Although **8b** was obtained as a single diastereomer in an enol form as indicated by its ^1H NMR spectrum, to rule out any undesired signals from other potential isomers, the labile stereogenic center linked to the carbonyl was destroyed by acetylation to give acetate **9** prior to performing NOE experiments.

(10) CCDC 701542 (**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 deposit@ccdc.cam.ac.uk.

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