First Tandem Radical Cyclization/Intramolecular Diels−Alder Reaction

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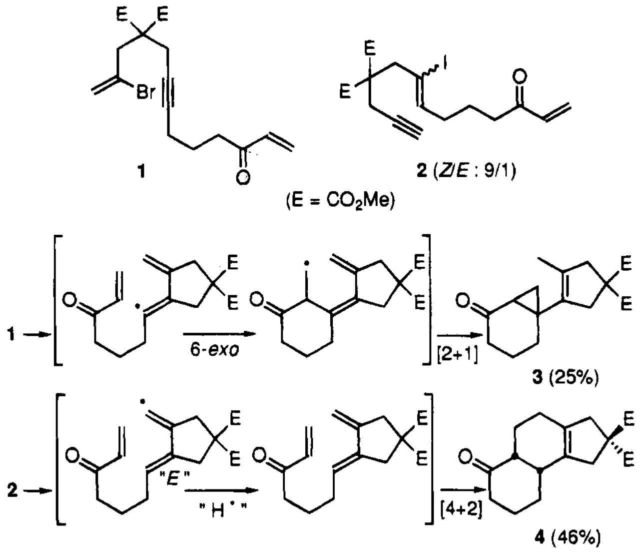
Summary: The first tandem radical cyclization/intramolecular Diels−Alder reaction has been achieved leading to a stereocontrolled synthesis of 6,6,5-membered tricyclic compounds from acyclic polyunsaturated substrates in a one-pot sequence. An initial 5-(*π-exo*)-*exo-dig* mode cyclization generated a vinylic carbon-centered radical which did not undergo further cyclization. After having been reduced, the diene intermediate reacted intramolecularly with a dienophile in a [4 + 2] cycloaddition reaction.

In the past few years, the complexity of target molecules has increased considerably which required chemists to find new methodologies allowing them to build a maximum of carbon−carbon bonds with minimal steps. This was successfully accomplished by the tandem radical reactions,[1] transition metal-catalyzed reactions, or pericyclic−pericyclic sequences,[2] but the radical−pericyclic sequence has not been yet investigated. Whereas the Diels−Alder reaction has been already used for the synthesis of compounds that are properly constituted to undergo radical cyclization,[3] we are unaware of previous examples in which both reactions were coupled in a one-pot sequence.

Herein, we want to report the first tandem radical cyclization/intramolecular [4 + 2] cycloaddition leading to the stereoselective synthesis of 6,6,5-membered tricyclic compounds in a one-pot reaction from acyclic substrates.

Very recently, we have disclosed a new [2 + 1] radical cycloaddition reaction from acyclic polyunsaturated compounds **1** generating a dienic radical intermediate which gave two consecutive 6-*exo-trig* and 3-*exo-trig* mode cyclizations to deliver in 25% yield **3**.[4] We then decided to examine the behavior of the same diene intermediate where the newly generated vinylic carbon-centered radical could not undergo further cyclization. After being reduced, this very reactive diene[5] would appear as a convenient substrate for an intramolecular [4 + 2] cycloaddition reaction[6] (Scheme 1).

Scheme 1



The study of this novel conceptual advance in the field of free-radical chemistry required the preparation of the trisubstituted vinylic iodide **2** which was efficiently synthesized, as a 9/1 unseparable mixture of *Z* and *E* isomers, in nine steps from 5-hexynal in 43% overall yield.[7] It is noteworthy that the stereochemistry of **2** should be without importance for the strategy described before. Indeed, *σ*-vinyl radicals have a very low barrier of inversion,[8] and the initial 5-(*π-exo*)-*exo-dig* cyclization process should lead mainly to the *E* trisubstituted exocyclic double bond.[9]

Compound **2** was treated by tributyltin hydride (1.5 equiv) with 0.1 equiv of AIBN in refluxing benzene (0.02 M) over a period of 16 h.[10] In these conditions, the tricyclic product **4** was isolated in 46% yield (60% based on recovered starting material) as a single stereomer.[11] As it was expected, the initially generated vinyl radical preferentially cyclized in the *Z* configuration to provide a dienic radical intermediate which was subsequently

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[2] (a) For a review see: Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (b) Aubert, C.; Gotteland, J. P.; Malacria, M. *J. Org. Chem.* **1993**, *58*, 4298−4305.

[3] (a) Ghosh, T.; Hart, H. *J. Org. Chem.* **1989**, *54*, 5073−5085. (b) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1990**, *55*, 1786−1792.

[4] Journet, M.; Malacria, M. *J. Org. Chem.* **1994**, *59*, 718−719.

[5] (a) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002−2021. (b) Gras, J. L.; Bertrand, M. *Tetrahedron Lett.* **1979**, 4549−4552. (c) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992−3993.

[6] For reviews see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10−23. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63−97. (c) Roush, W. R. Intramolecular Diels−Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon: New York, 1992; Vol. 5, pp 513−550.

[7] The details for the preparation of **2** will be described elsewhere.

[8] (a) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147−2195. (b) Singer, L. A.; Kong, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 5213−5219. (c) Kampmeier, J. A.; Fantazier, R. M. *J. Am. Chem. Soc.* **1966**, *88*, 1959−1964. (d) Journet, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 1893−1896. (e) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *32*, 6171−6197. (f) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969−980.

[9] (a) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529−4532. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829−2831. (c) Zahouily, M.; Journet, M.; Malacria, M. *Synlett* **1994**, 366−368.

[10] In a typical procedure, a benzene solution (5 mL) of n-Bu_3SnH (405 μL, 1.5 mmol) containing AIBN (14 mg, 0.1 mmol) was added by a syringe pump over 8 h to a solution of **2** (432 mg, 1.0 mmol) in refluxing benzene (50 mL) under nitrogen. After completion of the addition, the mixture was allowed to reflux for 8 additional hours. The solution was evaporated in vacuo to give a yellow oil which was chromatographed on silica with a mixture of petroleum ether and ether (1:1) as eluent (R_f = 0.30) to give 141 mg of **4** (46%).

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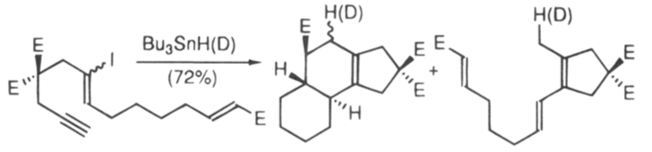
Scheme 2

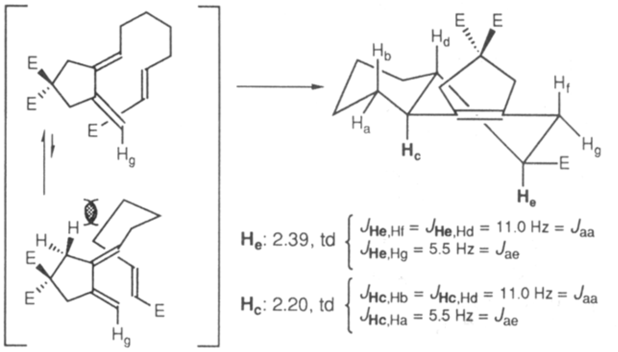


5 ($Z,E/E,E$: 6/4)
(E= CO_2Me)

6 (80)

7 (20)

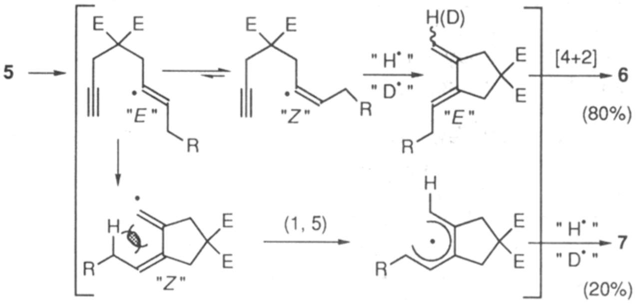
Scheme 3



$\mathbf{H_e}$: 2.39, td $\left\{ \begin{array}{l} J_{\mathbf{He},\mathrm{Hf}} = J_{\mathbf{He},\mathrm{Hd}} = 11.0\ \mathrm{Hz} = J_{\mathrm{aa}} \\ J_{\mathbf{He},\mathrm{Hg}} = 5.5\ \mathrm{Hz} = J_{\mathrm{ae}} \end{array} \right.$

$\mathbf{H_c}$: 2.20, td $\left\{ \begin{array}{l} J_{\mathbf{Hc},\mathrm{Hb}} = J_{\mathbf{Hc},\mathrm{Hd}} = 11.0\ \mathrm{Hz} = J_{\mathrm{aa}} \\ J_{\mathbf{Hc},\mathrm{Ha}} = 5.5\ \mathrm{Hz} = J_{\mathrm{ae}} \end{array} \right.$

Scheme 4



[R= $(CH_2)_3CH{=}CH\text{-}CO_2Me$]

reduced and then reacted in an intramolecular [4 + 2] cycloaddition reaction. Compound **4** was also accompanied by 10% of the corresponding reduced vinyl iodide and by 30% of unidentified products due to a polymerization of the very reactive enone as we had already observed in the case of the [2 + 1] cycloaddition reaction.[4] Importantly, the mixture of Z and E isomers (9/1) was unchanged in the recovered starting material (14%) indicating that the stereochemistry of **2** was effectively of no importance for our strategy.[12]

Nevertheless, in that case, there was a possibility that the formation of **4** was the result of a 10-*endo*/6-*exo* radical macrocyclization–transannulation process[13] although the stereoselectivity was in good agreement with the favored *endo*-like addition[5] according to the Alder rule. In order to prove the validity of this new tandem reaction, we next accomplished the cyclization of **5** ($Z,E/E,E$ = 6/4) where a 10-*endo-trig* mode cyclization cannot be involved.[14] The cyclization of **5** was performed with 1.2 equiv of Bu_3SnH under the same conditions as described before and proceeded cleanly to furnish a 4/1 unseparable mixture of **6** and **7** in 72% yield (Scheme 2). Once again, the tricyclic product **6** was isolated as a single stereomer which was the result of a favored *endo*-like addition *vs exo*-like one where a destabilizing interaction was developed for the latter as shown in Scheme 3. The relative stereochemistry was determined by the ^{1}H-NMR spectrum based on the J coupling constants (Scheme 3). A second experiment with Bu_3SnD showed that the dienic radical intermediate was not reduced stereoselectively, giving a 1/1 diastereomeric ratio, with an approach of the deuterium atom donor which was *anti* as well as *syn* to the E trisubstituted exocyclic double bond.[15] Interestingly, the initial vinyl radical did not cyclize exclusively in the Z configuration and led to the Z trisubstituted exocyclic double bond in part. Thus, a (1,5) hydrogen atom transfer occurred to provide the thermodynamically most stable trienic compound **7** (Scheme 4). This is, in our opinion, the first example of a (1,5) hydrogen shift from such a dienic radical. Finally, just like with the cyclization of **2**, when the reaction was conducted with less than 1 equiv of Bu_3SnH, the mixture of isomer ($Z,E/E,E$ = 6/4) was unchanged in the recovered starting material **5**.[12]

In conclusion, this new radical-pericyclic sequence may well lead for a general method for the stereocontrolled synthesis of many polycyclic molecules, and further investigations are under progress in our laboratory by using various dienophiles in order to define the scope of this strategy.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for **2** and **4**–**7** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) Prolonged time of **4** in $CDCl_3$ provided an epimerization leading to the formation of the thermodynamically most stable *trans*-fused decalone system. This epimerization has been previously reported (ref 5a,b).

(12) Kinetic studies for bromine abstraction by tributyltin hydride have shown that the rate for the E vinyl bromides was 4 times faster than for the Z ones. Therefore, the difference of reactivity between both isomers seems to be weaker for vinyl iodides. Curran, D. P.; Jasperse, C. P.; Totleben, M. J. *J. Org. Chem.* **1991**, *56*, 7169–7172.

(13) Very recently, a 10-*endo*/6-*exo* radical macrocyclization–transannulation process has been achieved from alkyl radicals to give the *trans*-fused decalone system. Pattenden, G.; Smithies, A. J.; Walter, D. A. *Tetrahedron Lett.* **1994**, *35*, 2413–2416.

(14) It has been shown that *endo* radical processes had to be achieved on α,β-unsaturated ketones for the cyclization of large rings (10–20 members). (a) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554–3560. (b) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9401–9403. (c) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843–4846.

(15) ^{1}H-NMR spectrum of **6** showed that the signal of He at 2.39 ppm (td, J = 11.0 and 5.5 Hz) was changed in a mixture of two signals indicating that the deuterium was in the equatorial position (He: 2.39, t, $J_{\mathrm{He,Hd}} = J_{\mathrm{He,Hf}} = J_{\mathrm{aa}}$ = 11.0 Hz) as well as the axial one (He: 2.39, dd, $J_{\mathrm{He,Hd}} = J_{\mathrm{aa}}$ = 11.0 Hz and $J_{\mathrm{He,Hg}} = J_{\mathrm{ae}}$ = 5.5 Hz).