LEWIS ACID PROMOTED TANDEM [4+2] CYCLOADDITION-REARRANGEMENT PROCESS--A SIMPLE AND EFFICIENT SYNTHESIS OF HIGHLY FUNCTIONALIZED OXABICYCLO[3.3.1]NONANES

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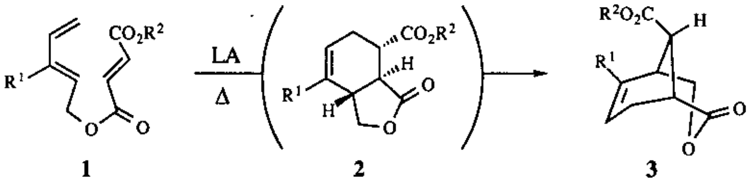
Abstract--Catalytic Lewis acid promoted tandem [4+2]cycloaddition-rearrangement processes of the trienic esters (**4**), (**8**) and (**9**) are reported. The novel tandem reactions proceed under thermal (110 °C, aluminum catalyst) conditions and afford the highly functionalized oxabicyclo[3.3.1]nonanes (**5**), (**10**) and (**11**), respectively.

The expeditious assembly of polycyclic ring systems from simple acyclic precursors with regio- and stereochemical control has for many years remained an important goal in organic synthesis. Tandem organic reactions[1] are among the most useful synthetic process, creating several bonds in a single step.

As an outgrowth of our interest in intramolecular Diels-Alder reactions of trienic esters,[2] we have been studying the tandem [4+2] cycloaddition-rearrangement process, a transformation which has significant potential for stereoselective synthesis of cyclic natural products.

Herein, we describe the results of preliminary studies on the Lewis acid promoted tandem [4+2] cycloaddition-rearrangement process (**1**→**2**→**3**).



Scheme I

An important advantage of the present strategy is that the required precursors are easily prepared by standard synthetic reactions involving the esterification of the appropriate carboxylic acids with the unsaturated alcohols in good yield.

We have carried out extensive studies on the tandem [4+2] cycloaddition-rearrangement chemistry of the trienic ester (**4**). The results, summarized in **Table I**, show that the outcome of the novel tandem reaction can be altered dramatically by varying the reaction conditions. First of all, we have examined Lewis acids[3] for the tandem process with the substrate (**4**)[4] in toluene or CH_2Cl_2 under argon. $EtAlCl_2$ and $TiCl_4$ are still totally reluctant to work for this purpose, however, Et_2AlCl, Et_2AlOEt and Et_2AlCN provided the desired product (**5**),[4] respectively (entries 3, 6, 7 and 9 in **Table I**) The product consisted of three isomers, (**5**), (**6**) and (**7**), which could be separated by column chromatography. Thermolysis of **4** at temperature ranging from 0 °C to 80 °C in the presence of Lewis acid showed no product formation. When the temperature was raised to 110 °C, the starting material (**4**) was consumed for 5 h to yield the highly functionalized oxabicyclo[3.3.1]nonane (**5**) in 48% yield[5] (entry 6 in **Table I**). Although this yield is not impressive, it should be noted that the above process (**4**→**5**) is a quite rare example of tandem pericyclic reaction-rearrangement sequence.[1] The low yields observed in entries 3, 6, 7 and 9 (**Table I**) may reflect the state of **4** rather than the tandem reaction since **4** was utilized without purification.

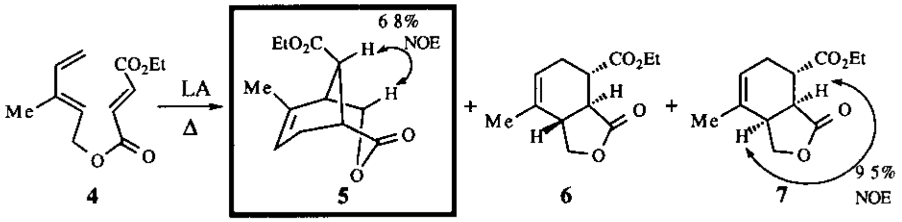


Table I Lewis Acid Promoted Tandem [4+2]Cycloaddition-Rearrangement Process of the Trienic Ester (4)

entry	Lewis acid (eq)	solvent (w/v%)	temp (°C)	time (h)	yield (%$^{a)}$)		
					5$^{b)}$	6$^{b)}$	7$^{b)}$
1	$EtAlCl_2$ (0.16)	toluene (5.0)	110	6.0	-	3	5
2	$EtAlCl_2$ (0.07)	toluene (1.8)	110	5.0	-	11	6
3	Et_2AlCl (0.20)	toluene(10.0)	110	9.5	44	4	15
4	Et_2AlCl (0.05)	toluene (1.9)	150$^{c)}$	3.5	-	20	10
5	Et_2AlCl (1.00)	CH_2Cl_2 (5.0)	0	2.5	-	-	-
6	Et_2AlOEt (0.20)	toluene (8.8)	110	5.0	48	4	15
7	Et_2AlOEt (0.05)	toluene (5.0)	150$^{c)}$	3.5	38	5	10
8	Et_2AlOEt (1.00)	CH_2Cl_2 (6.8)	15	19.0	-	-	-
9	Et_2AlCN (0.20)	toluene (8.7)	110	3.0	26	2	9
10	Et_2AlCN (0.20)	CH_2Cl_2 (4.9)	15	60.0	-	-	-
11	$TiCl_4$ (0.20)	toluene (4.7)	110	3.0	-	-	-
12	$TiCl_4$ (0.20)	CH_2Cl_2 (5.0)	40	3.0	-	-	-

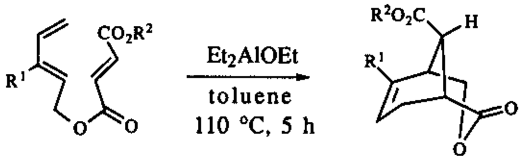
a) The sensitivity of the trienic ester (4) toward decomposition, hydrolysis on silica gel, led to their formation from the starting monoethyl fumarate and direct use in the tandem [4+2]- cycloaddition-rearrangement process without purification In addition, the yields of adducts were determined independently by isolation.

b) Stereochemistries of the products were established by two-dimentional nmr studies (COSY and NOESY).[6]

c) All thermal reactions were performed in sealed tubes using toluene as solvent.

In an effort to better understand the scope and usefulness of this process, we next examined the novel tandem [4+2] cycloaddition-rearrangement chemistry of several related substrates (**8** and **9**). Accordingly, compounds (**8**)[4,6] and (**9**)[4] were thermolyzed under similar reaction conditions to yield **10**[4] (45%) and **11**[4] (49%), respectively.

It is clear from the data that substituents R^1 and R^2 in **Scheme II** play a minor role in determining the reactivity of the tandem reaction.



R^1 = Br, R^2 = Et : **8**
R^1 = Me, R^2 = Me : **9**

R^1 = Br, R^2 = Et : **10** (45%)
R^1 = Me, R^2 = Me : **11** (49%)

Scheme II

A possible mechanism for the formation of the rearranged product (**5**) is shown in **Figure I**. Namely, Lewis acid coordinated to both ester and lactone carbonyl moieties of **6** to give **12**. This initially formed adduct then undergoes a lactone cleavage to the cation (**13**). The equilibration of the resultant cation (**13**) to **14**, and subsequent attack of the carboxylate group to the cationic carbon gave the thermodynamically favored bicyclic product (**5**).

In order to illustrate the synthetic potential of this new methodology, we have prepared the model compound (**16**),[4] featuring the bicyclic portion of C-aromatic taxane skeletons.[7]

In summary, we have shown that the combination of [4+2] cycloaddition and cationic rearrangement reaction is a powerful new methodology that allows ready access into a variety of oxabicyclo[3.3.1]nonanes.

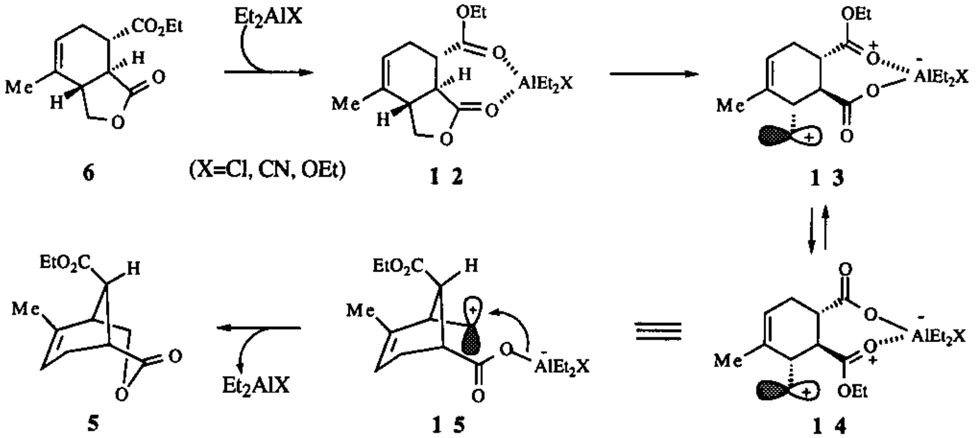
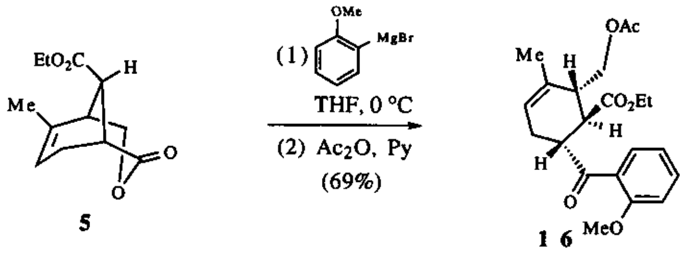


Figure I



Scheme III

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2. M. Toyota, Y. Wada, and K. Fukumoto, *Heterocycles*, 1993, **35**, 111.
3. The catalysts that seem to offer the best compromise between rate enhancement and suppression of diene polymerization were employed. W. R. Roush and S. M. Peseckis, *J. Am. Chem. Soc.*, 1981, **103**, 6696.
4. The structure assigned to all new compounds is consistent with the observed spectroscopic data (500 or 300 MHz ^{1}H nmr, ir, HRms). ^{1}H Nmr and Ir data for representative compounds are as follows: **compound (4)**: Ir (neat): 1730 and 1720 cm^{-1}. ^{1}H Nmr (300 MHz): δ 1.32 (3H, t, *J*=7.0 Hz), 1.84 (3H, s), 4.26 (2H, q, *J*=7.0 Hz), 4.84 (2H, d, *J*=7.0 Hz), 5.12 (1H, d, *J*=10.5 Hz), 5.28 (1H, d, *J*=17.6 Hz), 5.62 (1H, t, *J*=7.0 Hz), 6.39 (1H, dd, *J*=17.6 and 10.5 Hz), 6.86 (2H, s). **compound (5)**: mp 72.0 - 74.0 °C (n-hexane-Et$_2$O). Ir (neat): 1735 and 1730 cm^{-1}. ^{1}H Nmr (500 MHz): δ 1.26 (3H, t, *J*=7.4 Hz), 1.78 - 1.81 (3H, m), 2.23 - 2.30 (1H, m), 2.52 - 2.61 (1H, m), 2.79 (1H, br s), 3.00 (1H, dd, *J*=3.7 and 2.4 Hz), 3.32 - 3.36 (1H, m), 4.18 (2H, q, *J*=7.4 Hz), 4.34 (1H, dd, *J*=11.1 and 1.3 Hz), 4.41 (1H, dd, *J*=11.1 and 3.7 Hz), 5.50 - 5.53 (1H, m). **compound (8)**: Ir (neat): 1715 cm^{-1}. ^{1}H Nmr (500 MHz): δ 1.33 (3H, t, *J*=7.3 Hz), 4.27 (2H, q, *J*=7.3 Hz), 4.97 (2H, d, *J*=6.1 Hz), 5.34 (1H, d, *J*=10.4 Hz), 5.69 (1H, d, *J*=16.5 Hz), 6.17 (1H, t, *J*=6.1 Hz), 6.35 (1H, dd, *J*=16.5 and 10.4 Hz), 6.84 - 6.92 (2H, m). **compound (9)**: Ir (neat): 1730 and 1720 cm^{-1}. ^{1}H Nmr (300 MHz): δ 1.84 (3H, s), 3.81 (3H, s), 4.85 (2H, d, *J*=6.9 Hz), 5.12 (1H, d, *J*=10.5 Hz), 5.28 (1H, d, *J*=17.7 Hz), 5.63 (1H, t, *J*=6.9 Hz), 6.39 (1H, dd, *J*=17.7 and 10.9 Hz), 6.87 (2H, s). **compound (10)**: Ir (neat): 1730 and 1725 cm^{-1}. ^{1}H Nmr (300 MHz): δ 1.28 (3H, t, *J*=7.2 Hz), 4.12 - 4.28 (2H, m), 4.39 (1H, dd, *J*=11.4 and 3.6 Hz), 4.54 (1H, dd, *J*=9.1 and 0.6 Hz), 6.17 (1H, dd, *J*=4.5 and 2.4 Hz). **compound (11)**: mp 119.0 - 120.0 °C (n-hexane-Et$_2$O). Ir (neat): 1725 and 1710 cm^{-1}. ^{1}H Nmr (300 MHz): δ 1.80 (3H, s), 2.21 - 2.33 (1H, m), 2.49 - 2.61 (1H, m), 2.78 - 2.81 (1H, m), 3.00 - 3.05 (1H, m), 3.31 - 3.37 (1H, m), 3.73 (3H, s), 4.31 - 4.37 (1H, m), 4.39 (1H, dd, *J*=10.8 and 3.6 Hz), 5.50 - 5.53 (1H, m). **compound (16)**: Ir (neat): 1735, 1730 and 1670 cm^{-1}. ^{1}H Nmr (300 MHz): δ 1.19 (3H, t, *J*=7.0 Hz), 1.71 (3H, d, *J*=1.1 Hz), 2.04 (3H, s), 3.89 (3H, s), 4.02 - 4.11 (2H, m), 4.16 - 4.29 (2H, m), 5.57 - 5.61 (1H, m), 6.90 - 7.00 (2H, m), 7.39 - 7.47 (1H, m), 7.57 - 7.61 (1H, m).

5. In this thus far unoptimized reaction, *ca*. 10% of the over-reduction product during Lindlar reduction of (E)-3-methyl-2-penten-4-yl-1-ol was obtained along with varying degrees of urea. In addition, resubmission of accumulated **6** to tandem reaction provides more of compound (**5**).
6. The diene part of **8** was prepared by applying Roush's procedure.[8]
7. (a) M. Seto, K. Tsuruta, K. Morihira, T. Furukawa, Y. Horiguchi, and I. Kuwajima, Abstracts of 7th IUPAC Symposium on Organo-Metallic Chemistry directed towards Organic Synthesis, 1993, p.184. (b) *Idem*, Abstracts of 63th Symposium on Organic Synthesis, Japan, 1993, p. 99 and refs cited therein. (c) P. A. Wender and T. P. Mucciaro, *J. Am. Chem. Soc.*, 1992, **114**, 5878. (d) K. J. Shea, J. W. Gilman, C. D. Haffner, and T. K. Dougherty, *J. Am. Chem. Soc.*, 1986, **108**, 4953. (e) K. J. Shea and J. W. Gilman, *ibid.*, 1985, **107**, 4791. (f) K. J. Shea and P. D. Davis, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 419. (g) K. J. Shea and J. W. Gilman, *Tetrahedron Lett.*, 1983, **24**, 657. (1) Y.-F. Lu and A. G. Fallis, *Tetrahedron Lett.*, 1993, **34**, 3367. (2) Y.-F. Lu, C. W. Harwig, and A. G. Fallis, *J. Org. Chem.*, 1993, **58**, 4204, and refs cited therein.
8. W. R. Roush and K. Koyama, K. *Tetrahedron Lett.*, 1992, **33**, 6227.

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