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Construction of All-Carbon Quaternary Center by R_2AlCl−Mediated Ring-Opening Reaction of Oxacycles

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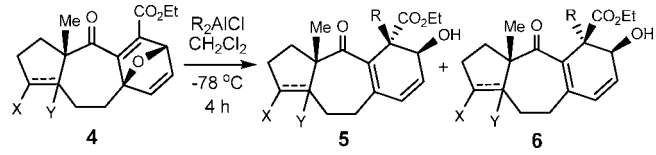
ABSTRACT



An unexpected R_2AlCl-mediated ring-opening reaction of oxacycles for the formation of all-carbon quaternary centers was discovered, and a possible mechanism is proposed. The developed chemistry provides a concise approach to synthesize structural diverse of dolastane-type compounds.

Diterpenoids represent an important family of natural products with promising antitumor and antibacterial activities. Three examples are dolatriol (**1**), amijiol (**2**), and guanacastepene A (**3**) (Figure 1).[2] Because of their importance as probes for evaluating biological processes and as leads for drug discovery, intensive efforts have been devoted to developing efficient strategies for their syntheses.[3]

In the context of our recent studies aimed at syntheses of dolastanes, we designed a concise strategy for the syntheses of **1** and amijiol **2** by using furan-tethered[4] intramolecular Diels−Alder reaction[5] and nucleophilic oxacyclic ring-opening reaction[6] as key steps (Figure 2).

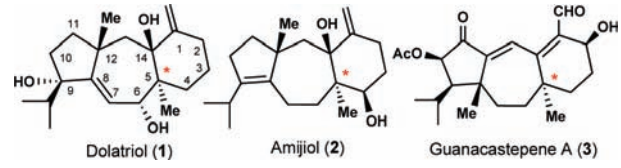


Figure 1. Naturally occurring diterpenoids.

To this end, we initiated a program to systematic study of the effect of nucleophilic reagents on the outcome of oxacyclic ring-opening reactions. Herein we report that **4** can be converted to **5** and **6** with R_2AlCl in a regioselective manner via an unexpected oxacyclic ring-opening reaction (Scheme 1).

The oxacyclic ring-opening reaction is a useful organic transformation, provided the regio-, stereo-, and chemoselectivities could be controlled. To quickly assess the proposed synthetic strategy for the formation of **A** from **B** (Figure 2),

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(1) (a) Pettit, G. R.; Ode, R. H.; Heralsd, C. L.; von Dreel, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677. (b) Ochi, M.; Watanabe, M.; Miura, I.; Taniguchi, M.; Tokoroyama, T. *Tetrahedron Lett.* **1980**, *21*, 1229. (c) Ochi, M.; Asao, K.; Kotsiki, H.; Miura, I.; Shibata, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 661.

(2) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116. (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

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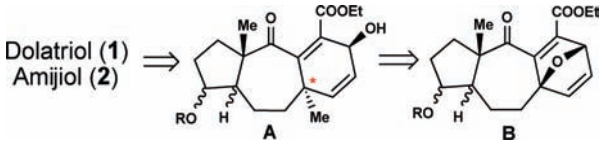
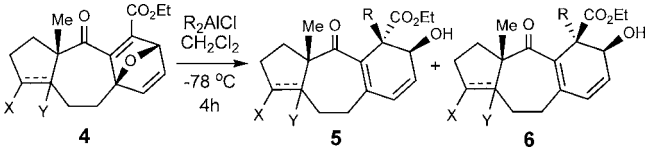


Figure 2. General synthetic strategy.

we selected **11** as a model to test its oxacyclic ring-opening reaction since **11** embodies the essential functional groups which are essential to the total synthesis of our target molecules.

Scheme 1. Ring-Opening Reaction of Oxacycles



Our synthesis commenced as outlined in Scheme 2. The commercially available ketone **7** was converted to **8** in 42% yield through diastereoselective alkylation of its carbonyl, followed by dehydration. An efficient hydroboration−oxidation−silylation sequence subsequently elaborated **8** into ester **9** in overall 43% yield in three steps. Ester **9** then underwent reduction and oxidation to give aldehyde **10**, which was then subjected to nucleophilic addition, followed by DMP oxidation to give the desired adduct **11** smoothly in 82% yield in

Scheme 2. Synthesis of Oxacycle **11**

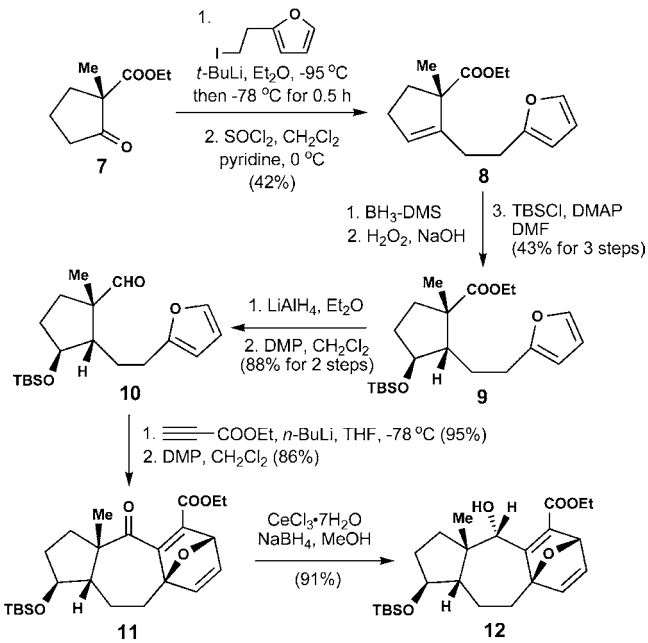
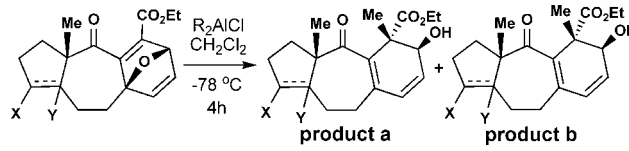


Table 1. Asymmetric Alkylations of Oxatricycles

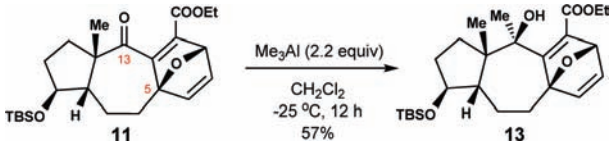


entry	SM	alkylating agent	product **a**	product **b**	yield (**a**/**b** ratio)
1	**11**	$AlEt_2Cl$	**18a**	**18b**	94%[a] (10:1)
2	**11**	$AlPr_3$ *t*-BuCl	**19a**	**19b**	90%[a] (10:7)
3	**11**	$AlBu_3$ *t*-BuCl	**20a**		86%[a]
4	**11**	$Al(i\text{-}Bu_3)$ *t*-BuCl	**21a**	**21b**	71%[b] (2:3)
5	**16**	Et_2AlCl	**22a**		66%[b]
6	**16**	$AlPr_3$ *t*-BuCl	**23a**	**23b**	74%[b] (3:1)
7	**16**	$AlBu_3$ *t*-BuCl	**24a**	**24b**	63%[b] (8:3)
8	**17**	Et_2AlCl	**25a**	**25b**	58%[b] (1:1)
9	**17**	$AlPr_3$ *t*-BuCl	**26a**	**26b**	67%[b] (3:4)
10	**17**	$AlBu_3$ *t*-BuCl	**27a**	**27b**	74%[b] (8:9)

16 **17**

[a] Oxatricycle (0.5 mmol) in CH_2Cl_2 (30 mL), R_2AlCl (1.25 mmol) at −78 °C for 4 h. [b] Oxatricycle (0.5 mmol) in CH_2Cl_2 (30 mL), ^{t}BuCl (2.0 mmol), R_3Al (2.0 mmol) at −78 °C for 4 h.

Scheme 3. Me_3Al-Mediated Stereoselective Methylation



two steps. The stereochemistry of **11** was confirmed by X-ray study of its derivative **12** prepared by Luche reduction.

Our initial studies for the ring-opening reaction utilized Me_3Al as alkylating agent due to our preliminary investigation[4b] that have demonstrated successes for similar substrates. However, when oxacycle **11** was reacted with Me_3Al in CH_2Cl_2 at −25 °C for 12 h, the undesired product **13** was obtained in 57% yield. The structure of **13** was verified by correlation of the NMR spectra and X-ray results of its close related analog (see Supporting Information for details).

The failure of the reaction prompts us to examine other alkylating agents for this reaction further. In our previous experiments, we observed a remarkable increase in the ring-opening reaction rate in the presence of small amounts of alkyl aluminum chlorides.[7] This observation, in addition to its higher oxygenophilic activation ability, led us to explore Me_2AlCl as the alkylating agent for the ring-opening reaction.[8] To this end, **11** was treated with Me_2AlCl in CH_2Cl_2 at −78 °C for 4 h, and to our surprise, product **14** with a newly generated all-carbon quaternary center at C1

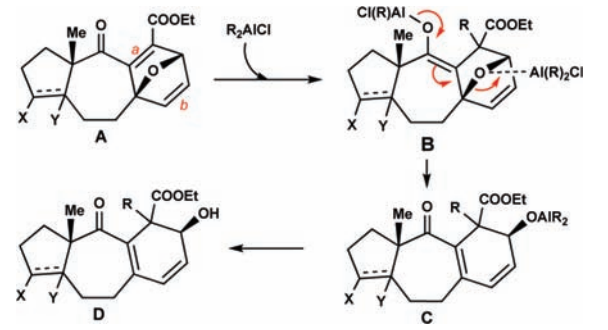


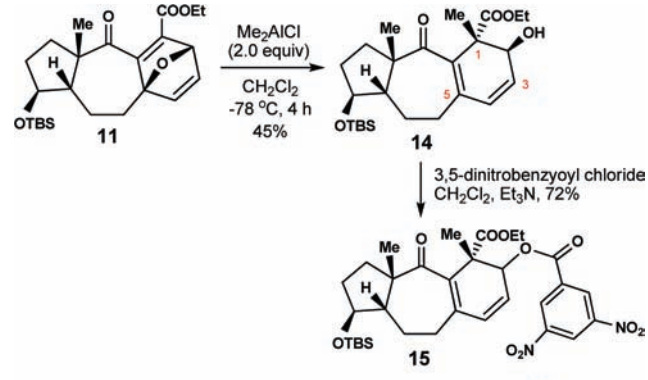
Figure 3. Mechanistic interpretation.

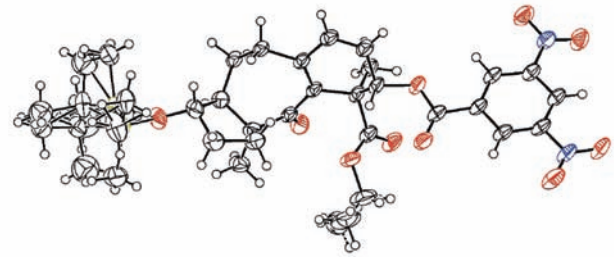
was obtained in 45% yield, and its structure was confirmed by X-ray study of its derivative **15**.

Given the unusual ring-opening reaction, we therefore decided to profile its reaction scope. To this end, other organoaluminium reagents, such as Et_2AlCl, Pr_2AlCl, Bu_2AlCl, and $^iBu_2AlCl$, were employed with compounds **11**, **16**, and **17** as the substrates (see Supporting Information for the syntheses of **16** and **17**), and their results were compiled in Table 1. Although we observed only product **14** in the previous **11**/Me_2AlCl system, we did isolate both diastereoisomeric products in good to excellent yields in all other systems listed except that of entries 3 and 5. Overall, the reactions are evidently regiochemically robust to create all-carbon quaternary center.

Mechanistically, while literature precedence implies the unsubstituted alkene might react first, the presence of two

Scheme 4. Ring-Opening Reaction of Oxacycles and X-Ray Structure of Compound **15**





X-ray structure of compound **15**

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(4) For application of furan-based Diels-Alder reaction to construct polycyclic ring system, see: (a) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *2*, 4418. (b) Brickwood, A. C.; Drew, M. G. B.; Harwood, L. M.; Ishikawa, T.; Marais, P.; Morisson, V. *J. Chem. Soc., Perkin Trans 1* **1999**, 913. (c) Li, C.-C.; Liang, S.; Zhang, X.; Xie, Z.; Chen, J.; Wu, Y.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709. (d) Liu, Y.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662. For a recent review on furan-based Diels−Alder chemistry, see: (e) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

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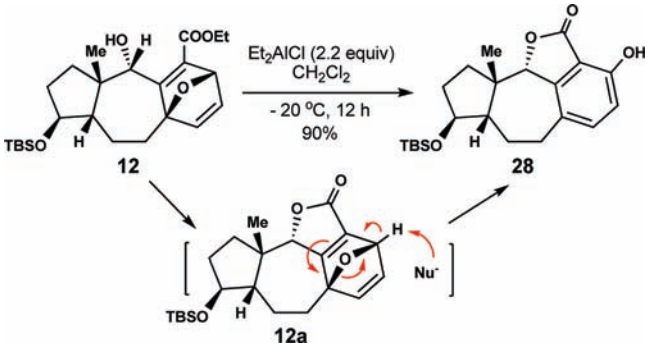
electron-withdrawing groups on the *tetra*-substituted alkene (*a*) might explain the observed regioselective alkylation on the alkene-a, rather then alkene-b (Figure 3).

We also envisaged that this reaction might proceed via the Lewis acid activated[9] conjugate addition of dialkylaluminum chloride to the enone, followed by ring-opening of the resulting aluminum enolate, and its regioselectivity could be interpreted at least in part by the fact that the enone is held in the s-cis orientation so that facilitates addition to enone moiety over the enoate.

To support this analysis, we then selected compounds **12** as the substrate to do the reaction under the conditions applied to the synthesis of **14** from **11** (Scheme 4). The experimental results indicated that the previous observed ring-opening reaction did not happen, and compound **12** was converted to its corresponding lactone **28** in 90% yield, presumably through the intermediate **12-a** (Scheme 5).

Scheme 5. Synthesis of Lactone **28**



In summary, we report here that R_2AlCl are unique and effective alkylating reagents to do the ring-open reaction of oxacycles by formal addition of nucleophiles to the stereohindrance carbons, thereby enabling all carbon quaternary centers to be constructed in a regioselective manner. The presented chemistry adds a new dimension to the oxacycles ring-opening chemistry and compliments to the existing methods in terms of both structural and stereochemical diversities, which opens new possibilities for strategic planning in complex-molecule synthesis.

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Supporting Information Available: Experimental (including spectra) and calculation (including coordinates) details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The small amounts alkyl aluminum chlorides presumably were generated *in situ* from reactions of trialkyl aluminum reagents with chlorinated solvents.

(8) (a) Mole, T.; Jeffery, E. A. *Organoaluminium Compounds*; Elsevier Publishing Company: Amsterdam, The Netherlands, 1972. (b) Kennedy, J. P.; Melby, E. G. *J. Org. Chem.* **1975**, *40*, 1099.

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