Stereospecific Cyclization of Vinyl Ether Alcohols. Facile Synthesis of (-)-Lardolure

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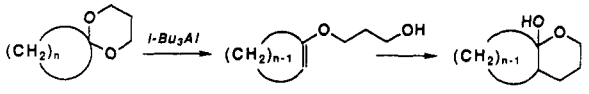
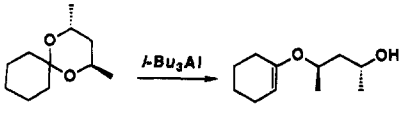
Summary: An efficient and stereospecific ring formation from unsaturated alcohols, which in turn are prepared by regio- and stereospecific ring opening of acetals, is described.

We report here a new method of ring formation that we believe has considerable potential in organic synthesis. We previously described that triisobutylaluminum is a powerful reagent for the transformation of acetal to vinyl ether (**1** → **2**).[1] It thus seemed to us that the possibility of forming rings by intramolecular addition of a terminal alcohol to a double bond, as shown in **2** → **3**, deserved to be explored.[2] This appeared particularly true because such a process would result in the formation of a ring that would have a variety of appendages with predictable stereochemistry.

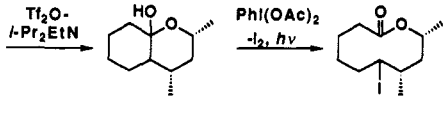


1 **2** **3**

Reaction of a solution of the acetal **4** with excess triisobutylaluminum at −78 °C for 0.5 h and 0 °C for 5 h produced the elimination product **5** in an essentially quantitative yield.[1] The crude vinyl ether thus obtained after extractive workup was exposed to triflic anhydride in dichloromethane in the presence of excess diisopropylethylamine at −78 °C for 3 h to produce, after workup with aqueous acetic acid, the cyclized hemiacetal **6** in >95% yield. Some of the results are summarized in Table I.



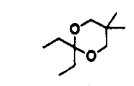
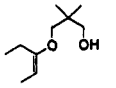
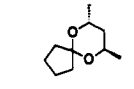
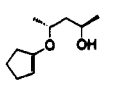
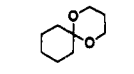
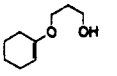
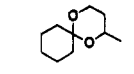
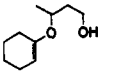
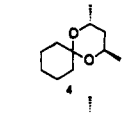
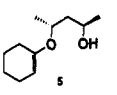
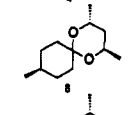
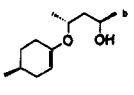
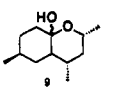
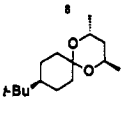
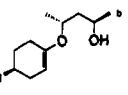
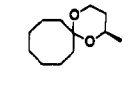
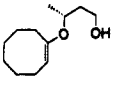
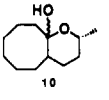
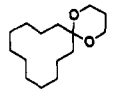
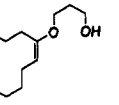
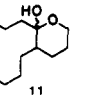
4 **5**



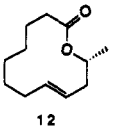
6 **7**

The produced hemiacetals were easily converted to lactones by the method of Suginome,[3] Suarez,[4] or Nagao.[5] For example, hemiacetal **6** was quantitatively transformed to the medium ring iodo lactone **7** (1.1 equiv of iodobenzene diacetate, 1.0 equiv of iodine in cyclohexane under irradiation at room temperature).[4] The method thus provides a facile route to large and medium ring lactones in a stereospecific way, which was demonstrated by the synthesis of (+)-recifeiolide (**12**)[6,7] from **10** (entry 8 of Table I) (photochemical ring opening followed by treatment with DBU) and exaltolide (15-pentadecanolide, **13**)[8] from **11** (entry 9) (photochemical ring opening followed by reduction with tributyltin hydride).

Table I. Intramolecular Cyclization of Vinyl Ether Alcohols

entry	acetal	vinyl ether[a]	hemiacetal[c]	yield, %
1				79
2				68
3				75
4				87
5				>95
6				>95
7				87
8				85
9				83

[a] The crude products were used for the next reaction without purification. [b] Diastereoratio of >9:1. See ref 8. [c] Mixture of anomers.



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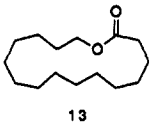

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We draw attention to the fact that in elimination of acetals derived from prochiral ketones (entries 6 and 7) with triisobutylaluminum, an asymmetric deprotonation

(1) Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444.
(2) Previous examples for cationic cyclization of vinyl ethers, see: Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192. Boeckman, R. K., Jr.; Bruza, K. J.; Heinrich, G. R. *Ibid. 1978*, **100**, 7101.
(3) Suginome, H.; Yamada, S *Tetrahedron* **1987**, *43* 3371.
(4) Freire, R.; Marrero, J. J.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **1986**, *27*, 383. **7** was mixture of two stereoisomers.
(5) Ochiai, M.; Iwaki, S.; Ukita, T.; Nagao, Y. *Chem. Lett.* **1987**, 133.
(6) $[\alpha]^{24}_D$ = +71.18° (*c* 1.03, $CHCl_3$) [lit.[7b] $[\alpha]_D$ = +70° (*c* 1, $CHCl_3$)].
(7) For (+)-recifeiolide, see: (a) Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rohwedder, W. K. *Can. J. Chem.* **1971**, *49*, 2029. (b) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755. (c) Utimoto, K.; Uchida, K.; Yamaya, M.; Nozaki, H. *Tetrahedron Lett.* **1977**, *41*, 3641.
(8) More recent examples for syntheses of exaltolide, see: Cossy, J.; Pete, J. P. *Bull. Soc. Chim. Fr.* **1988**, 989. Torra, N.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **1989**, *45*, 863. Matsuyama, H.; Nakamura, T.; Kamigata, N. *J. Org. Chem.* **1989**, *54*, 5218. Bestmann, H. J.; Schobert, R. *Synthesis* **1989**, 419.

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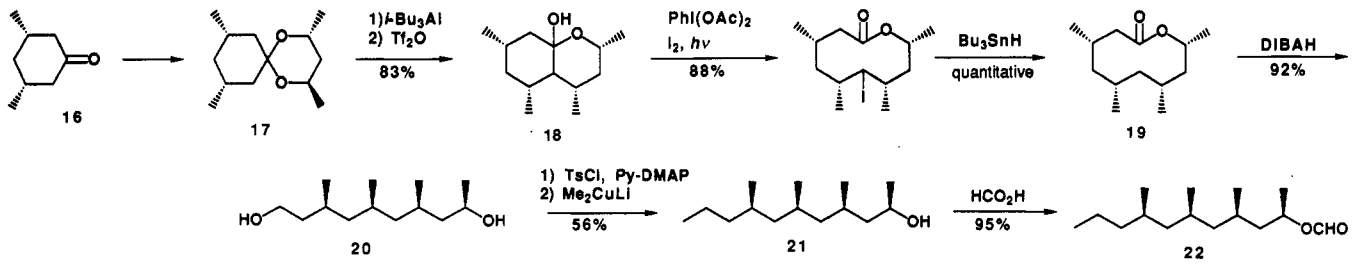
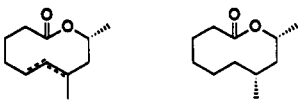
Scheme I



reaction takes place (selectivity: >9:1),[9] thus leading to optically pure hemiacetal after the cyclization process: Addition of triisobutylaluminum to the acetal **8** prepared from prochiral ketone followed by cyclization as above gave hemiacetal **9** (entry 6 of Table I). After one recrystallization of the crude product, all of the chiral centers of the molecule were found to be homogeneous (see also entry 7).

It is presumed that the annulation reaction proceeds through a pure S_N2-like mechanism, namely inversion of stereochemistry at the hydroxy function. Evidence for the complete inversion was obtained upon elimination (with DBU at 90 °C) followed by hydrogenation (Pd/C) from iodo lactone **7**. In this case, it was assumed that hydrogenation should give a mixture of diastereoisomers. Indeed, the crude reaction mixture from hydrogenation of **14** revealed two peaks on GC analysis, while exposure of the iodo lactone with tributyltin hydride–AIBN in THF under reflux furnished quantitatively lactone **15** as a sole product.



14 **15**

We now demonstrate the effectiveness of this approach starting with simple ketone **16**[10] which can be transformed into (−)-Lardolure (**22**),[11] the aggregation pheromone of the acarid mite, *Lardoglyphus Konoi*, in short steps (Scheme I). Under standard cyclization conditions the hemiacetal **18** was obtained in 83% yeild, mp 78–80 °C, after one recrystallization. Ring opening with iodobenzene diacetate gave the iodo lactone (88%), which was further transformed to lactone **19** quantitatively with tributyltin hydride. Addition of an excess of DIBAH at −78 °C produced the diol **20** (92%). Selective monotosylation (64%; 1.2 equiv of TsCl, pyridine–DMAP at −20 °C) followed by exposure of the monotosylate with excess dimethyl copper lithium in ether gave **21** in 92% yield with the desired carbon framework and desired stereochemistry. Formylation of **21** (95%; formic acid at 65 °C) then led to pheromone **22**,[12] which was identical with the authentic material kindly provided by Professor Kenji Mori.

The synthesis of **22** described herein is straightforward with full stereocontrol. Its brevity stems from the effective dovetailing of new annulation process.

Acknowledgment. A part of this work was financially supported by a Grant-in-Aid for Scientific Study from the Ministry of Education, Science and Culture of the Japanese Government. One of us (K.I.) is also acknowledged for the JSPS Fellowships for Japanese Junior Scientists. We also especially thank Professor Kenji Mori for the authentic sample of (−)-Lardolure.

Supplementary Material Available: Typical procedures and spectral data for new compounds (8 pages). Ordering information in given on any current masthead page.

(9) Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1363; *Tetrahedron* **1988**, *44*, 6021.

(10) Burman, M. J. F.; Elliott, D. R.; Gordon, M. H.; Robinson, M. J. T. *Tetrahedron Lett.* **1976**, *18*, 1535.

(11) For synthesis of Lardolure, see: Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5539; *Liebigs Ann. Chem.* **1987**, 555. For stereochemistry of Lardolure, see: Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5545.

(12) $[\alpha]^{25}_D$ = −3.64° (*c* 7.88, hexane) [lit.[11] $[\alpha]^{23}_D$ = −3.4° (*c* 7.86, hexane)]; GC analysis reveals a single peak and identical with an authentic sample;[11] t_R = 66.53 min (OV-101, capillary column at 100 °C), see ref 11.

Photolysis of Alkyl 4-Nitrobenzenesulfenates. A New and Versatile Method for the Generation of Free Radicals

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Summary: The irradiation of alkyl 4-nitrobenzenesulfenates with >300-nm wavelength light in benzene solution results in the homolytic cleavage of the O–S bond. The tertiary alkoxy radicals thus formed undergo β scission to produce carbon-centered free radicals in essentially quantitative yields which react with the arylthiyl radical to produce the alkyl aryl sulfide or dimerize. Primary and secondary alkoxy radicals undergo competitive disproportionation resulting in lower yields of the sulfide product.

In a study of the regioselectivity of reactions of substituted allyl radicals, it became necessary to find a method for the generation of such radicals in solution from convenient, readily available precursors. The use of peracid and peroxide derivatives and azo compounds did not appear to be an attractive approach due to the difficulty in

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