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Regiocontrol of Radical Cyclization by Lewis Acids. Efficient Synthesis of Optically Active Functionalized Cyclopentanes and Cyclohexanes

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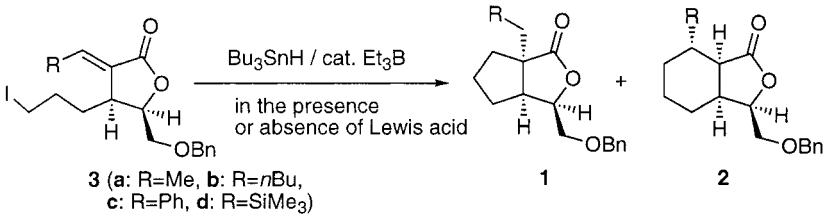
ABSTRACT



3 (**a**: R=Me, **b**: R=*n*Bu, **c**: R=Ph, **d**: R=SiMe$_3$) **1** **2**

Treatment of α-alkylidenelactones 3a–d with Bu_3SnH and a catalytic amount of Et_3B effected a 5-*exo* radical cyclization preferentially to provide the corresponding 1 and 2 in a ratio of 70:30 to 100:0. Meanwhile, the reaction of 3a and 3b in the presence of Et_2AlCl proceeded via a 6-*endo* cyclization pathway predominantly to afford 2a and 2b with 90% and 92% regioselectivity, respectively.

There are many biologically important compounds that have a chiral five- or six-membered carbocyclic ring in their structure as the main unit or a subunit, and thus, development of an asymmetric approach to these ring skeletons has attracted much interest. Herein reported is an efficient method for synthesizing optically active cyclopentane and cyclohexane compounds **1** and **2**, which have plural stereogenic centers. Compounds **1** and **2** might find utility as a chiral building block for synthesizing a variety of cyclopentanes and cyclohexanes, respectively, by taking advantage of the reactivity of the existing lactone functional group.

The characteristic features of our approach to **1** and/or **2**, which are summarized in Scheme 1 in a retrosynthetic way, involve an efficient synthesis of α-alkylidene lactones **3** by a Ti(II)-mediated intramolecular nucleophilic acyl substitution reaction of **6** (readily prepared from optically active epoxy alcohol derivative **4**) and the intramolecular radical cyclization of **3**, regiocontrolled by selection of the reaction conditions.[1]

The preparation of **3** was carried out according to the reaction sequence shown in Scheme 2. Thus, the Sharpless asymmetric epoxidation of (*E*)-6-(*tert*-butyldimethylsilyloxy)hex-2-ene-1-ol followed by protection of the hydroxy group as benzyl ether afforded **4** with 95% ee in 82% yield.[2] The epoxide ring opening of **4** with an acetylenic anion affording **5** under several different reaction conditions revealed that the conditions shown in Scheme 2 afforded the best and satisfactory regioselectivity. Thus, the ring-opening reaction of **4** with 2 equiv of RC≡CAlEt_2 in the presence of 1 equiv of Me_3Al in hexane proceeded with regioselectivity of 92:8, 95:5, 95:5, or 87:13, respectively, where R is Me, Bu, Ph, or $SiMe_3$.[3] The compound **5** was then converted to the ethyl carbonate **6**, which in turn was treated with a divalent titanium reagent Ti(O-*i*-Pr)$_4$/

(1) For radical-mediated substituted cycloalkane construction: Zhu, Q.; Qiao, L.-X.; Wu, Y.; Wu, Y.-L. *J. Org. Chem.* **1999**, *64*, 2428 and references therein.

(2) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

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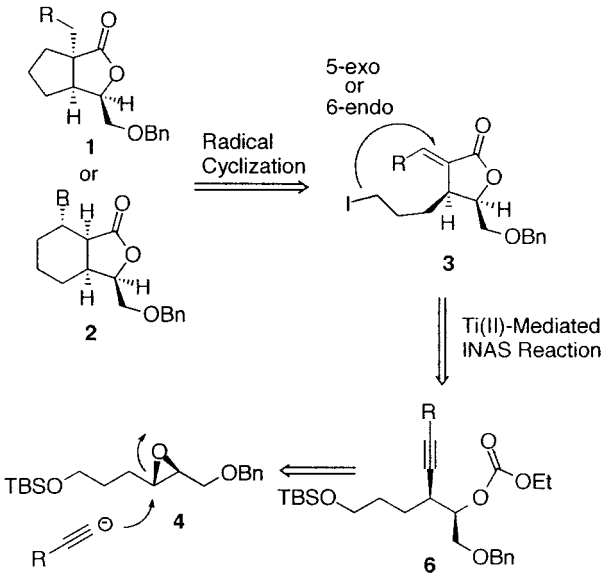
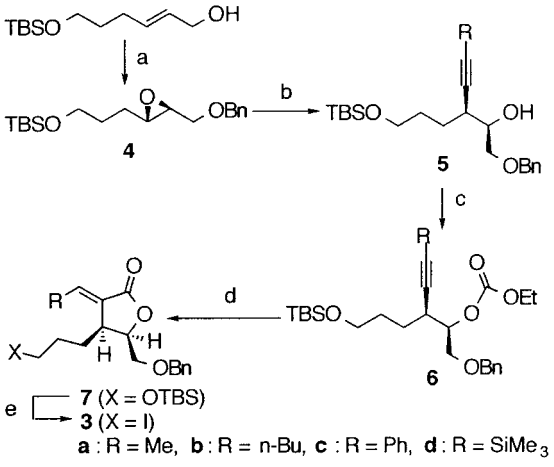
Scheme 1



2*i*-PrMgX[4] to afford, as expected, the intramolecular nucleophilic acyl substitution reaction product **7**.[5] From **7**, the compound **3** was prepared according to conventional reaction sequences. Although all transformations for conversion of **5** to **3** were carried out without separation of the regioisomer of **5**, the compounds **3** were obtained, after column chromatography, with >95% chemical purity (checked by ^{1}H NMR). Thus, in conclusion, the compounds **3**, where R is a methyl, butyl, phenyl, or trimethylsilyl group, i.e., **3a**, **3b**, **3c**, and **3d**, were prepared from **4** and the corresponding alkyne in 37%, 39%, 41%, and 39% overall yield, respectively.

Scheme 2[a]



[a]Conditions: (a) (i) Ti(O-*i*-Pr)$_4$, L(+)DIPT, TBHP, CH_2Cl_2; (ii) BnBr, NaH, THF, 82%; (b) RC≡CAlEt$_2$, Me$_3$Al, hexane, 77-81%; (c) $ClCO_2Et$, BuLi, THF, quantitative; (d) Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgCl, ether; (e) (i) aq. HF, THF; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) NaI, acetone

The results of radical cyclization of **3** thus produced using a Bu_3SnH/Et_3B reagent[6] are summarized in Table 1 (entries 1−4). It can be seen from the table that the substrates with an alkyl substituent at the sp^2-carbon, **3a** and **3b**, afforded a mixture of the corresponding **1** and **2** where the former was formed preferentially in a ratio of 70:30 for **3a** and 90:10 for **3b**. Meanwhile, the compounds **3c** and **3d** having a phenyl and a trimethylsilyl substituent, respectively, furnished only the 5-*exo* cyclized product **1**. The predominant or exclusive production of five-membered compounds **1** might be explained by the well-known fact that 5-*exo*-cyclization takes preference over 6-*endo*-cyclization for the radical cyclization reaction.[7] However, as radical addition to α,*β*-unsaturated carbonyl compounds has a tendency to proceed

Table 1. Radical Cyclization of **3**[a]

3 —(Bu_3SnH, cat. Et_3B)→ **1** + **2**

Entry	3	Solvent	1 : 2[b]	Combined Yield[c]
1	**a** ; R = CH_3	THF	70 : 30[d,e]	78%
2	**b** ; R = *n*-Bu	THF	90 : 10	92%[f]
3	**c** ; R = Ph	toluene	100 : 0[g]	85%
4	**d** ; R = TMS	toluene	100 : 0	84%
In the presence of Et_2AlCl[h]				
5	**a** ; R = CH_3	toluene	8 : 92[i]	86%
6	**b** ; R = *n*-Bu	toluene	10 : 90	86%

[a] Unless otherwise indicated, the reaction was carried out at 0 °C to room temperature. [b]Determined by GC and/or ^{1}H NMR analyses. [c]Isolated yield. [d]The reaction using AIBN in toluene instead of Et_3B in THF at 80 °C gave a **1**:**2** ratio of 60 : 40. [e]Use of EtOH or toluene as solvent instead of THF gave a **1**:**2** ratio of 70 : 30 or 55 : 45, respectively. [f]Uncyclized product (deiodinated product) was included in 16% yield (by GC), which could not be seperated by column chromatography. [g]Use of AIBN (80 °C) instead of Et_3B gave the same result. [h]The reaction was carried out at -78 °C to 0 °C. [i]The reaction at 0 °C to room temperature gave a **1**:**2** ratio of 18:82.

(3) The ring-opening reaction of the corresponding epoxy alcohol with BuC≡CAlEt$_2$ under the Nozaki conditions (Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597) proceeded in 60% yield with 70:30 regioselectivity, while the reaction of **4** with BuC≡CLi in the presence of a stoichiometric amount of BF_3·OEt$_2$ (Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391) or a catalytic amount of Me$_3$Al (Ooi, T.; Kagoshima, N.; Ichikawa, H.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 3228) did not take place.

(4) Reviews for synthetic reactions mediated by the titanium(II) reagent: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.

(5) For a Ti(II)-mediated synthesis of α-alkylidenelactones from alkynyl carbonates: Kasatkin, A.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6075. Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. Mincheva, Z. P.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7947.

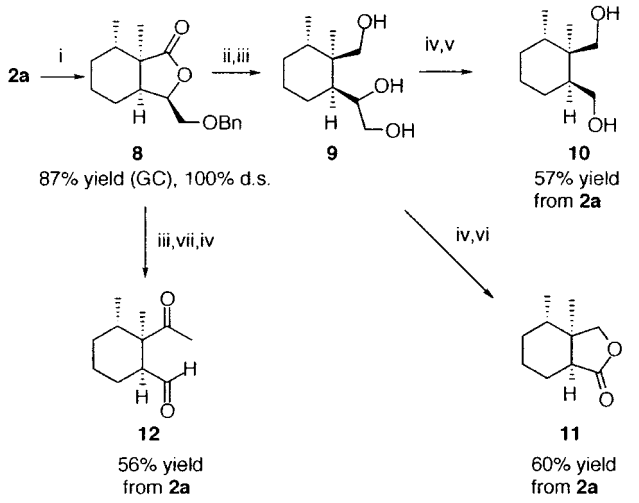
(6) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

via a conjugate addition pathway,[8] the reaction of **3** afforded conjugate addition products **2** also, though they are 6-*endo* cyclized products, and the amount of **2** was increased in proportion to the decrease of the steric requirement of the substituent R at the β-position of the carbonyl group from a phenyl or a trimethylsilyl to a butyl and to a methyl group as shown in Table 1.[9] Thus, in conclusion, the radical cyclization of **3** provided cyclopentanes **1** highly selectively or exclusively, except for the case where R is a methyl group. As the starting compounds **3** are readily preparable and the resulting **1** is highly functionalized, we believe that the present finding opens up a new efficient and practical access to five-membered carbocyclic compounds, even for the case where R is a methyl group.

With a selective conversion of **3** to cyclopentanes **1** in hand, our next concern was the possibility of their selective conversion to cyclohexane compounds **2**. Recently, radical reactions in the presence of Lewis acids have been investigated by several research groups,[10] including our group,[11] and it has been revealed that use of Lewis acids affects the reaction rates and the stereoselectivity. We anticipated that the regiochemistry of the radical cyclization of **3** might also be influenced by Lewis acids, although to the best of our knowledge, there are only two precedents for the case of intermolecular reaction[12] and no precedent for intramolecular reaction.[13] The results of the radical reaction in the presence of Et_2AlCl (1.5 equiv) are shown in entries 5 and 6 in Table 1. To our satisfaction, the cyclization of **3a** and **3b** proceeded with excellent regioselectivity of better than 90:10 furnishing the corresponding **2** as the major product; however, **3c** and **3d** did not afford the 6-*endo*-cyclized product at all.[14] The highly predominant production of a 6-*endo*-cyclized product from **3a** and **3b** might be explained by assuming that the complexation of the carbonyl group in **3** with Et_2AlCl increases the electron-withdrawing nature of the carbonyl group, thus making the conjugate addition pathway a lower-energy process.

In conclusion, a new efficient method for synthesizing optically active cyclopentanes **1** where R is an alkyl, aryl, or trimethylsilyl group and cyclohexanes **2** where R is an alkyl group has been developed. We believe that **1** and **2** might find wide use as starting compounds for synthesizing a variety of optically active five- or six-membered carbocycles including natural products. To show such possibility, we have prepared cyclohexane derivatives possessing a quaternary stereocenter, the construction of which has attracted much interest (Scheme 3).[15] Thus, successive

Scheme 3[a]



[a]Conditions: (i) LDA, MeI, THF; (ii) $LiAlH_4$, THF; (iii) H_2, Pd/C; (iv) $NaIO_4$, EtOH, H_2O; (v) $NaBH_4$, EtOH; (vi) PCC, CH_2Cl_2; (vii) MeLi, THF.

treatment of **2a** with LDA and MeI furnished the methylated lactone **8** as the sole diastereomer. From the compound **8**, triol **9**, diol **10**, lactone **11** and keto aldehyde **12** were prepared by conventional reaction sequences.[16] The diol **10** obtained here was reported to serve as a key intermediate for preparation of bakkenolides by Greene et al.,[17] and its spectroscopic data and $[\alpha]_D$ value ($[\alpha]^{25}_D$ +13.0 (*c* 0.62, $CHCl_3$), lit.[17b] $[\alpha]^{20}_D$ +13 (*c* 1.0, $CHCl_3$)) were in good agreement with those reported.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Review: Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(8) Review: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753. Selective 6-*endo*-cyclization of 5-carbomethoxy-5-hexenyl radicals via a conjugate addition pathway was reported: Della, E. W.; Kostakis, C.; Smith, P. A. *Org. Lett.* **1999**, *1*, 363. See also: Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. Tararov, V. I.; Kuznetzov, N. Y.; Bakhmutov, V. I.; Ikonnikov, N. S.; Bubnov, Y. N.; Khrustalev, V. N.; Saveleva, T. F.; Belokon, Y. N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3101.

(9) One reviewer suggested that regiospecific production of 5-*exo* product for the case of **3c** and **3d** might lie in product radical stability (such as benzyl and α-silyl radicals).

(10) Review for use of Lewis acids in radical reactions: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(11) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576. Urabe, H.; Kobayashi, K.; Sato, F. *J. Chem. Soc., Chem. Comm.* **1995**, 1043−1044.

(12) Vionnet, J.-P.; Schenk, K.; Renaud, P. *Helv. Chim. Acta* **1993**, *76*, 2490. Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274.

(13) In comparison with intermolecular reaction, a change in regioselectivity in intramolecular reaction seems to be more difficult, since it needs to overcome the stereoelectronic effect.

(14) The reaction mainly resulted in reduction of the olefin and iodo moieties.

(15) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

(16) Although the conversion of **2a** was carried out in the presence of 8% of **1a**, due to the difficulty of the separation by column chromatography, pure **10**, **11** and **12** were obtained after purification by column chromatography.

(17) (a) Greene, A. E.; Depres, J. P.; Coelho, F.; Brocksom, T. J. *J. Org. Chem.* **1985**, *50*, 3945, (b) Greene, A. E.; Coelho, F.; Depres, J. P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, *29*, 5661.