Pergamon

Tetrahedron Letters 43 (2002) 6511–6514

TETRAHEDRON LETTERS

Synthesis of carbo- and aza-bicyclo[4.3.0] and [4.4.0] compounds by Ti(II)-mediated cyclization of 2,7- or 2,8-enynyl-1-ol derivatives

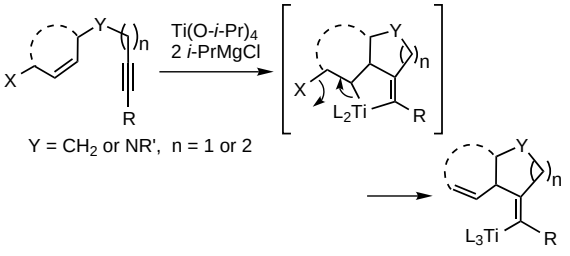
Yongcheng Song, Sentaro Okamoto† and Fumie Sato*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

Received 29 June 2002; revised 16 July 2002; accepted 18 July 2002

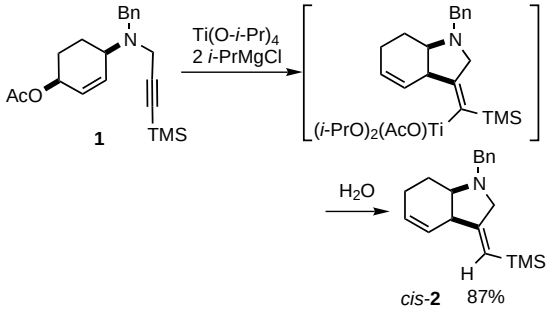
Abstract—The reaction of 2,7- and 2,8-enynyl-1-ol derivatives where the ene moiety is a part of a ring with a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent proceeds smoothly with excellent stereoselectivity to afford carbo- or aza-bicyclo[4.3.0] and [4.4.0] compounds, respectively, in high yields.

Cyclic compounds having carbo- and aza-bicyclo[4.3.0] and [4.4.0] structures as the main unit or a subunit are widely found in natural products,[1] and thus, much effort has been paid to develop new efficient methodology to prepare such structures. Among these methods, metal-catalyzed or -mediated cyclization reaction is very efficient and has attracted special interest.[2] Recently, we have reported that the cyclization of 2,7- and 2,8-enynyl-1-ol derivatives mediated by a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent proceeds as shown in Scheme 1 (without dashed line) via a titanabicyclic intermediate.[3,4] With these results, we were interested in extending this reaction to enynyl-1-ol substrates where the ene moiety is a part of a ring in expectation of opening up an easy access to bicyclic compounds with the structures mentioned above.



Scheme 1.

The reaction of *cis*-1-acetoxy-4-[(3-trimethylsilylprop-2-ynyl)benzylamino]-2-cyclohexene (**1**) with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl was found to proceed smoothly to give, after hydrolysis, hexahydroindole derivative **2** with *cis*-fused configuration in 87% yield (Eq. (1)), the structure of which was established by 2D NMR experiments (^{1}H–^{1}H COSY and NOESY); no *trans*-fused product was detected by ^{1}H NMR and GC analysis. It is noteworthy that starting from **1** with *trans*-configuration also afforded *cis*-**2** exclusively (see entry 2 in Table 1), indicating that the stereochemistry of the cyclization product does not depend on that of the leaving group.



(1)

With these results in hand, we then carried out the cyclization of several other representative substrates, and the results including those starting from **1** are summarized in Table 1. Besides the enyne **1**, diene substrate **3** was also well cyclized to give the corre-

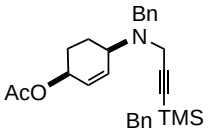
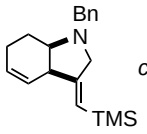
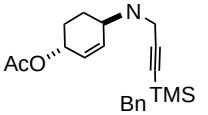
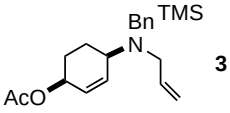
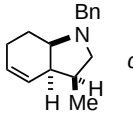
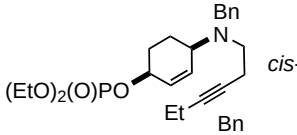
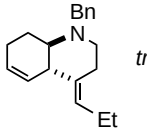
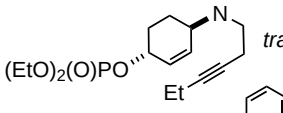
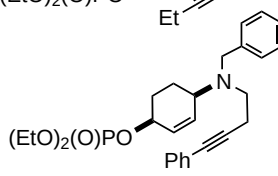
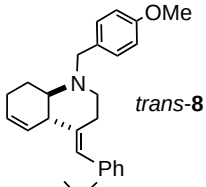
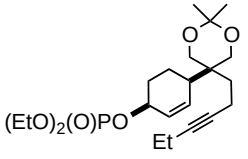
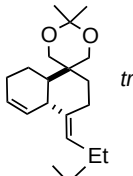
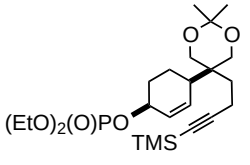
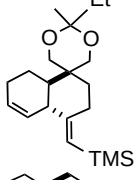
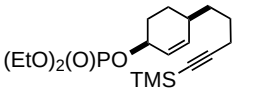
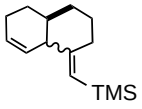
Keywords: bicyclo[4.3.0]; bicyclo[4.4.0]; Ti(II)-mediated cyclization.

* Corresponding author. Tel.: (+81)-(0)45-924-5787; fax: (+81)-(0)45-924-5826; e-mail: fsato@bio.titech.ac.jp

† Current address: Department of Applied Chemistry, Kanagawa University, 3-27-1 Rokkakubashi, Kanagawa-ku, Yokohama 221-8686, Japan.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01474-0

Table 1. Ti(II)-mediated cyclization of 2,7- or 2,8-enynyl-1-ol derivatives[a]

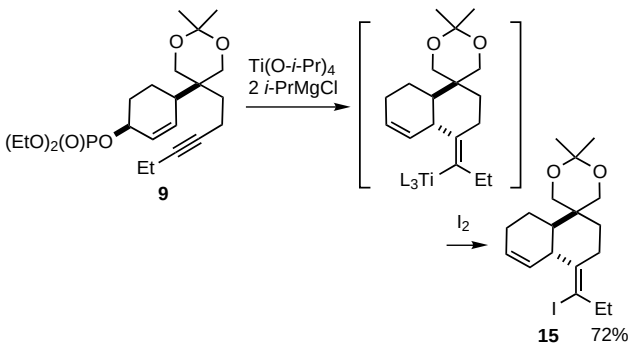
Entry	Starting Material	Product(s) [b]	Yield, %[c]
1	 **1**	 *cis*-**2**	87
2	 **1**[d]	*cis*-**2**	91
3	 **3**	 *cis*-**4**	65
4	 *cis*-**5**	 *trans*-**6**	87
5	 *trans*-**5**	*trans*-**6**	81
6	 **7**	 *trans*-**8**	79
7	 **9**	 *trans*-**10**	88
8	 **11**	 **12**[e] (*trans*:*cis* = 4.3:1)	85
9	 **13**	 **14** (isomeric ratio = 2:1)[f]	65[g]

[a] General procedure: to an ether solution of starting material (1.0 equiv.) and $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 equiv.) was added *i*-PrMgCl (1.3 M in ether, 2.4 equiv.) at -50 °C and the resulting mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched by addition of aqueous $NaHCO_3$. Upon filtration of precipitate, the solvent was removed and the product was purified by column chromatography. [b] All products showed satisfactory spectral data and the relative configuration was established by extensive NMR analysis unless otherwise stated. In all cases no olefinic isomer was produced. [c] Isolated yield unless otherwise noted. [d] *trans* : *cis* = 85 : 15. [e] The configuration of major product *trans*-**12** was confirmed by derivatization to authentic *trans*-octahydronaphthalene compound; see ref. 9. [f] The configuration was not determined. [g] NMR yield.

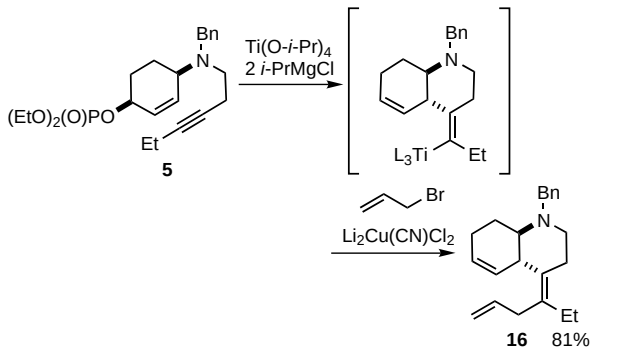
sponding azabicyclo[4.3.0] compound **4** with *cis*-fused configuration as a single diastereomer in good yield. The Ti(II)-mediated cyclization also can be successfully applied to prepare an azabicyclo[4.4.0] system as exemplified in the cyclization of 1-(diethylphosphoryl)oxy-4-[(hex-3-ynyl)benzylamino]-2-cyclohexene (**5**) and *cis*-1-(diethylphosphoryl)oxy-4-[(4-phenylbut-3-ynyl)(4-methoxybenzyl)amino]-2-cyclohexene (**7**). In these cases, however, the resulting octahydroquinolines **6** and **8** have *trans*-fused configuration, respectively, regardless of the stereochemistry of the starting compounds (entries 4 and 5). It should be noted that changing the leaving group of **5** from diethylphosphoryloxy to an acetoxy group resulted in a lower yield of **6** of 36%. As the starting substrates, such as **1**, **3**, **5**, and **7**, could be prepared by the substitution reaction of the readily accessible *cis*-1-acetoxy-4-chloro-2-cyclohexene[5] with the corresponding amine in high yields, the Ti(II) mediated cyclization reaction would provide an efficient synthesis of hexahydroindole and octahydroquinoline derivatives.

The reaction also enables the preparation of carbobicyclic compounds starting from 1-(diethylphosphoryl)oxy-4-(pent-4-ynyl)-2-cyclohexenes such as **9**, **11**, and **13**. Thus, cyclization of **9** produced octahydronaphthalene derivative **10** as shown in entry 7 in Table 1. The compound **10** thus obtained has *trans*-fused configuration exclusively. However, the substrates **11** and **13**, which have a sterically-demanding trimethylsilyl group as an acetylenic substituent, co-produced the corresponding *cis*-fused octahydronaphthalene (entries 8 and 9).

Although Table 1 summarizes the hydrolysis outcome after the Ti(II)-mediated cyclization, as the reaction products contain a titanium–carbon bond, they could be further manipulated by treatment with other electrophiles,[4] which would provide additional flexibility in synthetic planning. Thus, upon completion of the cyclization of **9**, the product was reacted with iodine to afford the corresponding alkenyliodide **15** in 72% yield (Eq. (2)). Likewise, the cyclization product of **5** was allylated in the presence of $Li_2Cu(CN)Cl_2$ to give the corresponding triene **16** in 81% yield (Eq. (3)).[6]

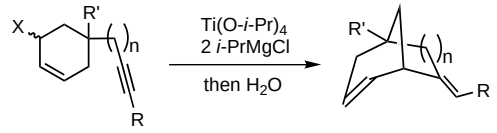


(2)



(3)

As part of our attempts to broaden the scope of this Ti(II)-mediated cyclization, we investigated the reaction of 5-alkynylcyclohex-2-en-1-ol derivatives such as **17a**, **17b**, and **17c** as shown in Eq. (4). However, only the compound **17b** was cyclized to give bicyclo[3.2.1] compound **18b** in 46% yield.[7] It appears that, in comparison with the formation of bicyclo[4.*n*.0] ($n=4$ and 3), cyclization to construct the bicyclo[3.*n*.1] ($n=3$ and 2) structure mediated by the Ti(II) reagent is much more difficult probably due to the steric factors. Nevertheless, from the synthetic viewpoint, new access to compounds having the bicyclo[3.2.1] structure with a quaternary bridgehead carbon is noteworthy.[8] Further investigations of the Ti(II)-mediated cyclization reaction to reveal its scope and limitation as well as the mechanistic rationale are underway in our laboratory.



17a: R=Et, n=2, R'=$CH_2OTBDMS$, X=$OP(O)(OEt)_2$, OC(O)OEt, OMe, or Cl — **18a** 0%
17b: R=Et, n=1, R'=$CH_2OTBDMS$, X=Cl — **18b** 46%
17c: R=Bu, n=1, R'=H, X=Cl or $OP(O)(OEt)_2$ — **18c** 0%

(4)

Acknowledgements

We thank the Ministry of Education, Culture, Sports, Science and Technology (Japan) for financial support and the Japan Society for the Promotion of Science (JSPS) for a grant to Y.S.

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6. Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245.
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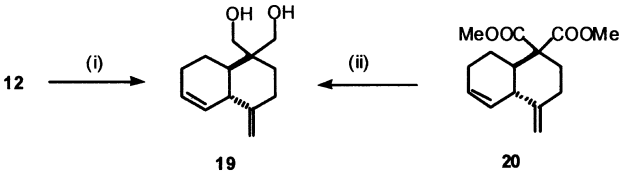
9. The configuration of the major product *trans*-**12** was confirmed by derivatization to the authentic *trans*-1,1-di(hydroxymethyl)octahydronaphthalene **19**, which was prepared by reduction of the known compound *trans*-**20** [Oppolzer, W.; Gaudin, J.-M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705].



Reagents and conditions: (i) 1N HCl/THF, 75%; (ii) $LiAlH_4$, 85%.