Tetrahedron Letters 55 (2014) 6907-6910

Contents lists available at ScienceDirect

**Tetrahedron Letters** 

journal homepage: www.elsevier.com/locate/tetlet

# Stereoselective synthesis of chiral hydrocarbazoles via the catalytic Diels–Alder reaction of siloxyvinylindole and cyclic Z-olefin



Tetrahedroi

Keisuke Yoshida, Takahiro Morikawa, Naoto Yokozuka, Shinji Harada, Atsushi Nishida\*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan

### ARTICLE INFO

Article history: Received 13 September 2014 Revised 9 October 2014 Accepted 17 October 2014 Available online 24 October 2014

Keywords: Catalytic Diels–Alder reaction Scandium triflate Chiral hydrocarbazole Silyl enol ether Stereoselective alkylation

## ABSTRACT

The catalytic Diels–Alder reaction of siloxyvinylindole and cyclic Z-olefin derived from pyroglutamic acid gave optically active substituted hydrocarbazoles. The *exo/endo* selectivity of this reaction could be controlled by using an appropriate Lewis acid. Scandium triflate gave high *exo*-selectivity and copper triflate gave moderate *endo*-selectivity. Subsequent stereoselective alkylation of the cycloadduct led to the synthesis of highly substituted hydrocarbazoles with five continuous chiral centers including a quaternary carbon.

© 2014 Elsevier Ltd. All rights reserved.

# Introduction

Hydrocarbazoles are important moieties in biologically active compounds, such as strychnine  $(1)^1$  and opiate analog  $2^2$  (Fig. 1). Due to their biological properties, methods for the stereoselective synthesis of optically active and highly substituted hydrocarbazoles are valuable in the fields of organic and medicinal chemistry. The Diels-Alder reaction using indole derivatives is one of the most powerful synthetic tools for the construction of a hydrocarbazole scaffold.<sup>3</sup> Recently, we reported the enantioselective synthesis of substituted hydrocarbazoles by a chiral holmium complex-catalyzed Diels-Alder reaction of siloxyvinylindoles 3 with acyclic Eolefins 4 (Scheme 1, Eq. 1).<sup>4</sup> This reaction proceeded *exo*-selectively to afford optically active substituted hydrocarbazoles 5 possessing an anti-configuration depending on the configuration of the dienophile. In the total synthesis of strychnine, a syn-oriented hydrocarbazole would be required as a synthetic intermediate. Therefore, we designed cyclic Z-olefin 6 derived from pyroglutamic acid as a dienophile to obtain hydrocarbazole 7 possessing a syn-configuration (Scheme 1, Eq. 2).<sup>5</sup> To the best of our knowledge, Diels-Alder reactions using pyroglutamic acid-derived lactam as a dienophile under thermal conditions only gave *endo*-adducts.<sup>6</sup> To obtain **7**, this Diels-Alder reaction should proceed in an exo-selective manner.



Figure 1. Selected examples of biologically active compounds that contain hydrocarbazole.

We report here (1) the synthesis of optically active substituted hydrocarbazoles by a catalytic Diels–Alder reaction of siloxyvinylindole with cyclic *Z*-olefin, (2) the control of *exo/endo* selectivity in this reaction through the use of an appropriate Lewis acid, and (3) the construction of a quaternary carbon by stereoselective alkylation of the cycloadduct.

### **Result and discussion**

Designed cyclic *Z*-olefin was prepared as shown in Scheme 2. Starting from *D*-pyroglutamic acid **8**, alcohol **9** was obtained by esterification, protection of nitrogen, and reduction. Benzylation of **9** and exchange of the *N*-protecting group yielded methyl carbamate **11**. Introduction of an olefin moiety into **11** was accomplished by syn- $\beta$ -elimination of sulfoxide to give cyclic *Z*-olefin **12**.

We treated **12** with siloxyvinylindole **3** (1.5 equiv) under thermal conditions (toluene, 110 °C, 8 h) as an initial trial. However, cycloadducts were not obtained at all (Table 1, entry 1).<sup>7</sup>



<sup>\*</sup> Corresponding author. Tel./fax: +81 43 226 2942. E-mail address: anishida@faculty.chiba-u.jp (A. Nishida).



**Scheme 1.** Diels–Alder reaction of siloxyvinylindole **3** with acyclic *E*-olefin **4** or cyclic *Z*-olefin **6**.



**Scheme 2.** Reagents and conditions (a) SOCl<sub>2</sub>, MeOH; (b) PMBCl, KI, NaH, THF, 0–50 °C; (c) NaBH<sub>4</sub>, EtOH/THF, 68% for 3 steps; (d) BnBr, NaH, THF; (e) CAN, aq MeCN, 84% for 2 steps; (f) CICO<sub>2</sub>Me, NaH, THF, 93%; (g) PhSSPh, LiHMDS, THF, -78 °C, 85%; (h) *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (i) PPh<sub>3</sub>, toluene, 110 °C, 81%, for 2 steps.

Next, several metal triflates were tested to promote this Diels-Alder reaction. First, we investigated the catalytic conditions (25 mol % of catalyst, rt, 3 days) by using Lewis acids such as aluminum, copper, zinc, and scandium triflates, which are known to promote Diels–Alder reactions.<sup>8</sup> As a result, the expected Diels–Alder reaction proceeded in the presence of a catalytic amount of Lewis acid to afford a separable mixture of exo-adduct 13 and endoadduct 14. The reactions with aluminum triflate and copper triflate showed endo-selectivity (entries 2 and 3). When zinc triflate was used, exo-adduct 13 and endo-adduct 14 were obtained in similar amounts (entry 4). On the other hand, the reactions with scandium triflate exhibited moderate exo-selectivity (entry 5). Next, we investigated the catalytic effects of lanthanide triflates because of their unique properties due to the specific coordination numbers (entries 6–9).<sup>9</sup> As a result, exo-adduct **13** was obtained in the highest yield with the use of thulium triflate.

The stereochemistry of both cycloadducts was determined by NMR experiments, as shown in Figure 2. The regioselectivity of this Diels–Alder reaction was identical to that in our previous report<sup>4</sup> and no regioisomer was observed.

With thulium triflate and scandium triflate, the effects of the solvent were tested, as shown in Table 2. Higher *exo*-selectivity was observed when carbon tetrachloride or THF was used as a solvent (entries 2 and 6). However, the yield of cycloadducts was dramatically decreased with the use of THF. No improvement was

#### Table 1

Screening of Lewis acid for the Diels-Alder reaction



Entry	Catalyst	Yield (13+14, %)	Ratio ( <b>13:14</b> ) <sup>b</sup>
1 <sup>a</sup>	_	No reaction	_
2	Al(OTf) <sub>3</sub>	12	10:90
3 <sup>c</sup>	$Cu(OTf)_2$	91	23:77
4	$Zn(OTf)_2$	41	52:48
5	$Sc(OTf)_3$	70	88:12
6	Yb(OTf) <sub>3</sub>	62	79:21
7	$Tm(OTf)_3$	89	83:17
8	$Er(OTf)_3$	77	80:20
9	Ho(OTf) <sub>3</sub>	69	79:21

<sup>a</sup> Thermal conditions: toluene, 110 °C, 8 h.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> Reaction time was 1 day.



Figure 2. Key HMBC and NOE correlations of cycloadducts.

Table 2

Effects of solvent and reaction time in the Diels-Alder reaction

3 +	+ 12 catalyst (25 mol %) solvent rt, reaction time		ol %) → ime	<b>13</b> (exo-adduct) <sup>+</sup>	<b>14</b> (e <i>ndo</i> -adduct)		
Entry	Catalyst	Solvent	Time (d)	Yield ( <b>13+14</b> , %)	Ratio ( <b>13:14</b> ) <sup>a</sup>		
1	$Tm(OTf)_3$	CHCl <sub>3</sub>	3	64	85:15		
2	Tm(OTf)₃	CCl <sub>4</sub>	3	69	92:8		
3	Tm(OTf) <sub>3</sub>	1,2-DCE	3	75	78:22		
4	Tm(OTf)₃	PhCl	3	76	81:19		
5	Tm(OTf)₃	Toluene	3	48	85:15		
6	Tm(OTf)₃	THF	3	23	91:9		
7	Tm(OTf)₃	$CH_2Cl_2$	6	95	84:16		
8	$Tm(OTf)_3$	CCl <sub>4</sub>	6	90	93:7		
9	Sc(OTf) <sub>3</sub>	CCl <sub>4</sub>	3	70	94:6		
10	$Sc(OTf)_3$	$CH_2Cl_2$	6	95	88:12		
11	$Sc(OTf)_3$	CCl <sub>4</sub>	6	98	95:5		
<sup>a</sup> Determined by <sup>1</sup> H NMR.							



Figure 3. Plausible transition states for the exo- and endo-adducts

observed with the use of other solvents instead of dichloromethane (entries 1, 3–5). The yield of cycloadducts increased with an increase in the reaction time from 3 days to 6 days (entries 7 and 8).

The combination of scandium triflate with carbon tetrachloride showed higher *exo*-selectivity (entry 9). The yield of cycloadducts also increased with an increase in the reaction time when scandium triflate was used as a catalyst (entries 10 and 11). Although this Diels–Alder reaction required rigorous dried conditions and a long reaction time, as shown in the Experimental section, *exo*-adduct **13** could be obtained selectively in high yields.

The plausible transition states for this Diels–Alder reaction are shown in Figure 3. Lewis acid activated a dienophile by forming a coordinated complex to promote the Diels–Alder reaction. The face selectivity of this Diels–Alder reaction could be perfectly controlled by the chiral center of the dienophile and both cycloadducts were obtained via the *exo-* or *endo-*transition states, respectively. Generally, the *endo-*transition state is preferred to the *exo-*transition state due to the secondary orbital interaction, and *endo-*adducts will be obtained predominantly.

Aluminum and copper triflates promoted this Diels–Alder reaction and showed good to moderate *endo*-selectivity. However, the *endo*-transition state would be destabilized by the steric repulsion between diene and the coordinated complex. The difference in energy between the *endo*-transition state and the *exo*-transition state may not be large enough because of the steric repulsion in the *endo*-transition state, and a more bulky complex would be most likely to promote this reaction *exo*-selectively. On the other hand, thulium and scandium triflates showed high *exo*-selectivity.



**Scheme 3.** Stereoselective alkylation for the construction of a chiral quaternary carbon.

These metals are capable of coordinating with the dienophile, solvent, or product due to their high coordination numbers. The resulting coordinated complex became more bulky, and high *exo*-selectivity was observed as a result of retarding the secondary orbital interaction.<sup>10</sup>

The high *exo*-selectivity with THF was also explained by the formation of a more bulky coordinated complex. However, the Lewis basicity of THF decreased the reactivity of Lewis acid and the yield of cycloadducts was dramatically decreased. On the other hand, carbon tetrachloride gave good results with respect to *exo*-selectivity without a decrease in the yield. In general, the dipole moment of the *endo*-transition state is greater than that of the *exo*-transition state. García and Mayoral co-workers reported that a polar solvent stabilizes the *endo*-transition state to increase *endo*-selectivity.<sup>11</sup> In our case, the *endo*-transition state could not be stabilized with the use of carbon tetrachloride as a nonpolar solvent and the Diels–Alder reaction proceeded *exo*-selectively.

Interestingly, an increase in the reaction time slightly increased *exo*-selectivity. The carbonyl moieties of cycloadducts are likely to coordinate with a Lewis acid such as scandium or thulium triflate and a more bulky complex would be formed. This complex could increase *exo*-selectivity due to its bulkiness, although reactivity seemed to be lower.<sup>12</sup>

A chiral quaternary carbon center was constructed by stereoselective alkylation of the silyl enol ether moiety, as shown in Scheme 3. When *exo*-adduct **13** was treated with several alkyl halides and tetrabutylammonium fluoride at -78 °C for 10 min, the corresponding alkylated products were obtained as a single diastereomer in good yields. Especially, cyanomethylated compound **15d** could be a potential synthetic intermediate of strychnine.<sup>13</sup> Sequential reactions including the Diels–Alder reaction and stereoselective alkylation represent an effective method for constructing a hydrocarbazole bearing five continuous chiral stereocenters including a quaternary carbon.<sup>14,15</sup>

# Conclusion

We have synthesized optically active and highly substituted hydrocarbazoles by the catalytic Diels–Alder reaction of siloxyvinylindole with cyclic Z-olefin. *Exo/endo* selectivity could be controlled by using an appropriate Lewis acid. In particular, scandium triflate affords *exo*-adduct **13** and copper triflate provides *endo*-adduct **14**. Moreover, both enantiomers of cycloadducts could be easily obtained by using a dienophile derived from D- or L-pyroglutamic acid. Therefore, according to our method, all of the enantiomers and diastereomers of the Diels–Alder adducts could be stereoselectively synthesized with the use of a suitable dienophile and Lewis acids. Alkylation of the silyl enol ether moiety of *exo*-adduct **13** proceeded smoothly at -78 °C. In all cases, the alkylated products were obtained as a single diastereomer with a quaternary chiral carbon center in high yields. The further transformation of cyanomethylated compound **15d** to strychnine is in progress.

# Experimental

### **General procedure**

Sc(OTf)<sub>3</sub> (75 µmol) in a test tube with a stirring bar was heated at 90 °C under reduced pressure (<0.1 mmHg) for 30 min. After being allowed to cool to room temperature, the test tube was charged with dry argon and CCl<sub>4</sub> (distd from CaCl<sub>2</sub>, 0.5 mL) was added. The reaction vessel was cooled to 0 °C and a solution of **12** (300 µmol) and **3** (450 µmol) in CCl<sub>4</sub> (distd from CaCl<sub>2</sub>, 0.6 mL + 0.4 mL to rinse) was added. Next, the mixture was warmed to room temperature and stirred for 6 days. The reaction mixture was quenched by the addition of H<sub>2</sub>O. The water layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The volatile materials were removed under reduced pressure and the resulting residue was purified by column chromatography (SiO<sub>2</sub>, hexane/AcOEt = 4/1 to 2/1) to give a mixture of *exo*-adduct **13** and *endo*-adduct **14** as a white foam. Their ratio was confirmed by <sup>1</sup>H NMR (Table 2, entry 11).

This mixture could be separated by silica gel column chromatography (CHROMATOREX<sup>\*</sup>-DIOL (Fuji Silysia Chemical Ltd.), hexane/AcOEt = 4/1) to give *exo*-adduct **13** and *endo*-adduct **14**.

*exo*-Adduct **13**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.06–1.08 (m, 18H), 1.14–1.24 (m, 3H), 2.03–2.11 (m, 1H), 2.23 (d, *J* = 4.0, 15.6 Hz, 1H), 2.58–2.64 (m, 1H), 3.28–3.78 (m, 2H), 3.79 (s, 3H), 3.90 (s, 3H), 4.00 (d, *J* = 3.2, 6.4 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.58 (s, 2H), 4.73 (t, *J* = 2.4 Hz, 1H), 6.93–6.99 (m, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.28–7.38 (m, 5H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  13.58, 17.85, 17.87, 33.89, 34.89, 47.98, 53.78, 55.41, 60.40, 61.15, 68.73, 73.43, 110.76, 114.01, 114.68, 123.49, 123.54, 127.08, 127.27, 127.52, 127.69, 127.74, 128.45, 131.17, 137.50, 141.63, 143.73, 152.29, 163.41, 173.51; IR (neat) 2943, 1787, 1720, 1593, 1354, 1261, 1164, 1090, 1013 cm<sup>-1</sup>; HRMS (ESI) *m*/*z* calcd for C<sub>40</sub>H<sub>50</sub>N<sub>2</sub> O<sub>8</sub>SSiNa [M+Na]<sup>+</sup> 769.2955, found 769.2957; [α]<sub>D</sub><sup>20</sup> +5.86 (*c* 1.00, CHCl<sub>3</sub>).

endo-Adduct **14**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.03–1.08 (m, 18H), 1.11–1.22 (m, 3H), 2.20 (d, *J* = 17.2 Hz, 1H), 2.67–2.82 (m, 2H), 3.61 (d, *J* = 6.0, 9.6 Hz, 1H), 3.68 (d, *J* = 3.2, 9.6 Hz, 1H), 3.71 (s, 3H), 3.80 (s, 3H), 3.97 (d, *J* = 2.4, 10.0 Hz, 1H), 4.01 (d, *J* = 4.4, 8.0 Hz, 1H), 4.55–4.59 (m, 3H), 6.88–6.95 (m, 3H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.29–7.36 (m, 5H), 4.44 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.61, 17.79, 17.91, 31.07, 35.85, 45.29, 53.33, 55.48, 62.12, 64.55, 69.77, 73.44, 112.40, 114.19, 114.57, 123.05, 123.39, 127.30, 127.70, 127.81, 127.83, 128.49, 129.36, 129.59, 137.58, 141.51, 143.26, 151.82, 163.21, 170.08; IR (neat) 2943, 1752, 1714, 1594, 1346, 1258, 1159, 1090, 1011 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>40</sub>H<sub>50</sub>N<sub>2</sub>O<sub>8</sub>SSiNa [M+Na]<sup>+</sup> 769.2955, found 769.2936;  $[\alpha]_{\rm P}^{20}$  –8.69 (*c* 1.02, CHCl<sub>3</sub>).

# Acknowledgments

This work was supported by JSPS KAKENHI (Grant Numbers 26•3297 (TM), 25460006 (SH), and 25293001 (AN)) and the Takeda Science Foundation – Japan (SH).

#### **References and notes**

- Hendrickson, J. B. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VI, pp 179–195.
- 2. Welsh, W. J.; Yu, S. J.; Nair, A. WO Patent 2004026819, 2004.
- For 3-vinylindoles (a) Saroja, B.; Srinivasan, P. C. Synthesis 1986, 748; (b) 3 Murase, M.; Hosaka, T.; Koike, T.; Tobinaga, S. Chem. Pharm. Bull. 1989, 37, 1999; (c) Pindur, U.; Lutz, G.; Fischer, G.; Schollmeyer, D.; Massa, W.; Schröder, L. Tetrahedron 1993, 49, 2863; (d) Bleile, M.; Wagner, T.; Otto, H.-H. Helv. Chim. Acta 2005, 88, 2879; (e) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. Angew. Chem., Int. Ed. 2008, 47, 9236; (f) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III J. Am. Chem. Soc. 2011, 133, 12354; For 2-vinylindoles: (g) Eitel, M.; Pindur, U. J. Org. Chem. 1990, 55, 5368; (h) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. J. Am. Chem. Soc. 2009, 131, 13606; (i) Cao, Y.-J.; Cheng, H.-G.; Lu, L.-Q.; Zhang, J.-J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. Adv. Synth. Catal. 2011, 353, 617; (j) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. Nature 2012, 475, 183; For other recent strategies: (k) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. J. Am. Chem. Soc. 2011, 133, 15212; (1) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. Org. Lett. 2012, 14, 1310; (m) Xiao, Y.-C.; Zhou, Q.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. Org. Lett. 2012, 14, 5940; (n) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-I.; Ishibashi, H. Angew. Chem., Int. Ed. 2013, 52, 906; (o) Xiao, Y.-C.; Yue, C.-Z.; Chen, P.-Q.; Chen, Y.-C. Org. Lett. 2014, 16, 3208.
- 4. Harada, S.; Morikawa, T.; Nishida, A. Org. Lett. **2013**, *15*, 5314.
- 5. Isomerization of acyclic *Z*-olefin **16** was observed under Lewis acid-catalyzed Diels–Alder conditions (unpublished result).

- (a) Ohfune, Y.; Tomita, M. J. Am. Chem. Soc. 1982, 104, 3511; (b) Bailey, J. H.; Cherry, D. Y.; Crapnell, K. M.; Moloney, M. G.; Shim, S. B.; Bamford, M. J.; Lamont, R. B. Tetrahedron 1997, 53, 11731; (c) Oba, M.; Nishiyama, N.; Nishiyama, K. Chem. Commun. 2003, 776; (d) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. Tetrahedron 2006, 62, 5223.
- The Diels-Alder reaction of siloxyvinylindole 3 with 17 proceeded under thermal conditions to give *exo*-adduct 18 and *endo*-adduct 19 (unpublished result).



- (a) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* 2000, 717, 200–202;
  (b) Reymond, S.; Cossy, J. *Chem. Rev.* 2008, 108, 5359. and, references cited therein.
- (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. Chem. Rev. 2002, 102, 2227; (b) Ladziata, U. ARKIVOC 2014, 307.
- Exo selective Diels–Alder reaction could be also explained by the substitution pattern of the reactants (a) Lam, Y.-H.; Cheong, P. H.-Y.; Mata, J. M. B.; Stanway, S. J.; Gouverneur, V.; Houk, K. N. *J. Am. Chem. Soc.* 2009, 131, 1947; It was also reported that certain metals with less coordination numbers promoted the *exo-selective Diels–Alder reaction. For example*, (b) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron* 2002, 58, 9903. See also references in 10(a).
- Cativiela, C.; García, J. I.; Gil, J.; Martínez, R. M.; Mayoral, J. A.; Salvatella, L.; Urieta, J. S.; Mainar, A. M.; Abraham, M. H. J. Chem. Soc., Perkin Trans. 2 1997, 653.
- 12. As control experiments, a mixture of *exo*-adduct **13** and *endo*-adduct **14** was treated under catalytic conditions. The ratio of **13** and **14** in the resulting solution did not change at all. When pure **13** was also treated under the same conditions, no **14** was observed from the resulting solution. According to these experiments, isomerization between *exo* and *endo* isomers should be excluded.
- 13. Beemelmanns, C.; Reissig, H.-U. Angew. Chem., Int. Ed. **2010**, 49, 8021. 14. The one-pot synthesis of **15d** from **12** was achieved in 53% yield.
- The one-pot synthesis of **15d** from **12** was achieved in 53% yield.
  Thulium triflate can be recycled and reused. (1st: yield 89%, *exo/endo* = 83:17, 2nd: yield 77%, *exo/endo* = 81:19.)