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Chemistry

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Journal:	<i>Organic &amp; Biomolecular Chemistry</i>
Manuscript ID	OB-COM-07-2024-001143.R1
Article Type:	Communication
Date Submitted by the Author:	05-Aug-2024
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## COMMUNICATION

# Ring-closing metathesis of dialkenylcycloalkanes for the synthesis of fused bicycloalkanes and tricycloalkanes

Received 00th January 20xx,  
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

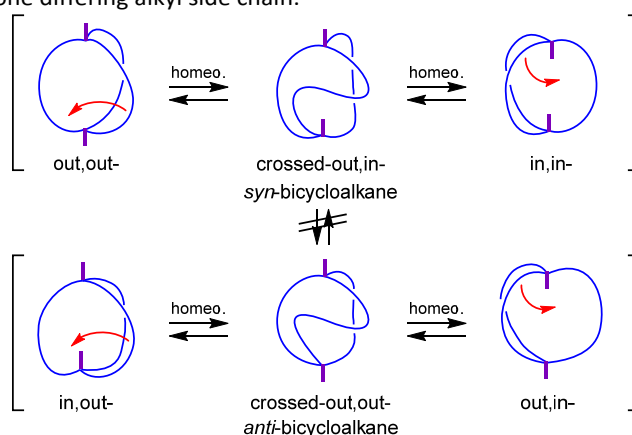
**Ring-closing metathesis of dialkenyldisilacycloalkane using the Grubbs catalyst, followed by hydrogenation, afforded a mixture of two disilabicycloalkanes and tetrasilatricycloalkanes. This method can synthesize a diastereomer mixture of disilabicycloalkanes with one differing alkyl side chain. The observed symmetries of the NMR spectra of *anti*-bicycloalkanes depend significantly on the length of the side chain. The findings may contribute to the molecular design of functional bicycloalkanes based on structural transformations of the stable forms.**

## Introduction

Research on the structural chemistry of fused bicycloalkanes (BCAs) and their analogues has been extensively conducted due to their unique cage structures.<sup>1,2</sup> Notably, large-scale and flexible BCAs display unique topological structural chemistry, such as homeomorphic conversions between certain conformers (Fig. 1).<sup>1,2</sup> In these BCAs, two diastereomers exist, namely *syn*- and *anti*-BCAs,<sup>1</sup> each exhibiting different spatial symmetries in the orientations of the bridgehead substituents in non-crossed forms (Fig. 1).

Understanding the most stable conformer in large-scale BCAs has been partially revealed due to their flexible molecular skeleton. Recently, our group reported the synthesis and structures of dimethyldisilabicyclo[n.n.n]alkanes (n = 10, 14, and 18), and the homeomorphic conversion between in,out- and out,in-forms in *anti*-bicyclo[10.10.10]alkane was observed as an exchange between in- and out-methyls in temperature-dependent NMR studies.<sup>1,3</sup> These results have prompted us to investigate the structures and dynamics of

bicyclo[18.10.10]alkane to elucidate the structural effects of one differing alkyl side chain.



**Fig. 1.** Homeomorphic conversions in bicycloalkanes (BCAs).

Several coupling strategies between alkenyls using the ring-closing metathesis (RCM) reaction<sup>4</sup> for the synthesis of BCAs and related compounds with carbon,<sup>5</sup> silicon,<sup>3,6,7</sup> phosphorus<sup>8-13</sup> or arsine<sup>14</sup> bridgeheads and flexible long alkyl side chains have been reported. Herein, the intramolecular coupling of dialkenyldisilacycloalkane for the synthesis of BCAs was investigated. Pioneering work using the related carbon analogue for the synthesis and crystal structures of out,out-bicyclo[8.8.8]hexacosane was reported by Mash and co-workers,<sup>5</sup> and the analysis of the desired out,out-structure was fully completed except for the byproducts. One of the remarkable features of this strategy is that a diastereomer mixture of fused BCAs with one differing alkyl side chain, such as [18.10.10]-derivatives, can be synthesized by designing the lengths of the alkenyl chains of the precursor. Moreover, tricycloalkanes (TCAs) were also formed and characterized in the present work.

## Results and discussion

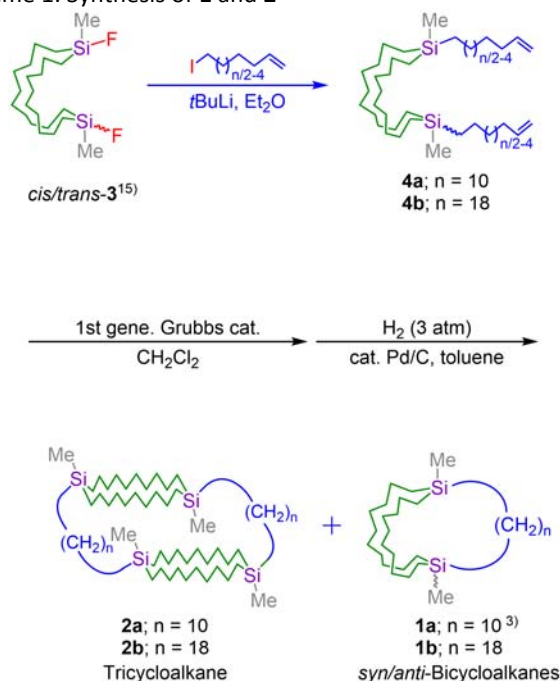
A mixture of diastereomers of bicyclo[n.10.10]alkanes **1a** (n = 10) and **1b** (n = 18) was synthesized according to Scheme 1. In this study, a *cis/trans* mixture of 1,11-difluoro-1,11-

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<sup>†</sup> Electronic Supplementary Information (ESI) available: [Synthetic Details, Copies of NMR and HRMS Spectra for All New Compounds, Details of Temperature-Dependent NMR Study, and Details of X-ray Crystallography. CCDC 2367922, 2367923, and 2369099]. See DOI: 10.1039/x0xx00000x

dimethyldisilacyclodocosane **3**<sup>15</sup> was used as a starting material, with the *cis/trans* ratio determined by <sup>19</sup>F NMR signal intensities (Fig. S1) shown in Table 1. Additionally, the signal assignment of the *trans*-**3** in <sup>19</sup>F NMR was carried out by measuring the solution of the pure *trans*-isomer, whose structure was confirmed by X-ray crystallography (Fig. S33). The reaction of the *trans*-rich mixture of **3**<sup>15</sup> (Table 1) with alkenyllithium, prepared from the corresponding 1-iodoalkene and tert-butyllithium, yielded a *cis/trans* mixture of dimethyldialkenyldisilacycloalkane **4**. This mixture was used for the subsequent reaction, as the *cis/trans*-isomers could not be isolated separately. Unfortunately, their ratio remained unclear due to the lack of separation in the NMR signals. The ring-closing metathesis (RCM) reaction of the mixture, using the 1st generation Grubbs catalyst for 2 days followed by hydrogenation, afforded a mixture of products. After flash column chromatography to remove insoluble materials, the product mixture was subjected to recycling gel permeation chromatography (GPC). Recycling GPC charts (RI-detector) of the crude product mixture in the reaction of **4a** are shown in Fig. 2. Three fractions, namely A, B, and C, were obtained. Each fraction, in order of retention time, contained polymers (Fraction A), TCAs (Fraction B), and two BCAs (Fraction C), respectively, as their identifications are discussed later. Almost the same GPC chart of the crude products in the reaction of **4b** was obtained, as shown in Fig. S2.

Scheme 1. Synthesis of **1** and **2**Table 1. Isolated Yields for the Synthesis of **1** and **2**

Entry	Reactant	<i>cis/trans</i> ratio of <b>3</b> <sup>a)</sup>	Product Isolated Yield		
			<b>2</b>	<i>syn</i> - <b>1</b>	<i>anti</i> - <b>1</b>
1	<b>4a</b>	1/17	30%	1.7%	8.6%
2	<b>4b</b>	1/26	8%	5%	23%

a) determined by <sup>19</sup>F NMR signal intensities shown in Fig. S1.

The TCA was also obtained as an almost pure compound (purity: more than 80%) in Fraction B, as the <sup>1</sup>H NMR spectrum revealed only a small amount of impurities, such as other isomers. The structure of the main tricycloalkane was obtained as single crystals and identified by X-ray crystallography. Fig. 3 displays the molecular structures of tricycloalkanes **2a** and **2b**. The structure having alkyl-chains linkages between two *trans*-cycloalkanes was observed. In solution, the methyl (Me) signals in both <sup>1</sup>H and <sup>13</sup>C NMR spectra each exhibit a single singlet (Fig. 4ab, showing chemical shifts of  $\delta_H$  -0.10 and  $\delta_C$  -4.7 for **2a**, and  $\delta_H$  -0.11 and  $\delta_C$  -4.9 for **2b**, respectively), indicating that the *trans*-dimethyldisilacyclodocosane moieties are undergoing facile rotation within the molecular frame.

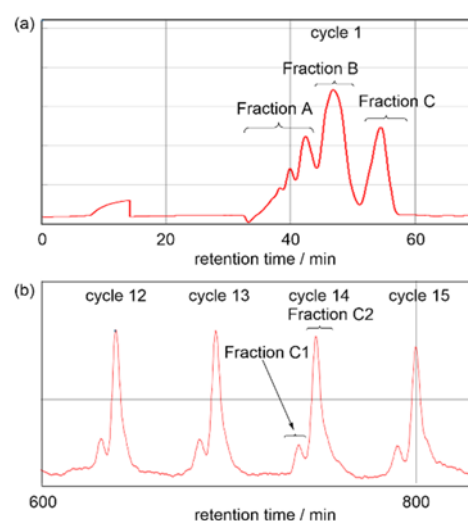


Fig. 2. Recycling GPC charts (RI-detector) of the crude product mixture in the synthesis of bicyclo[10.10.10]alkane (Entry 1 in Table 1).

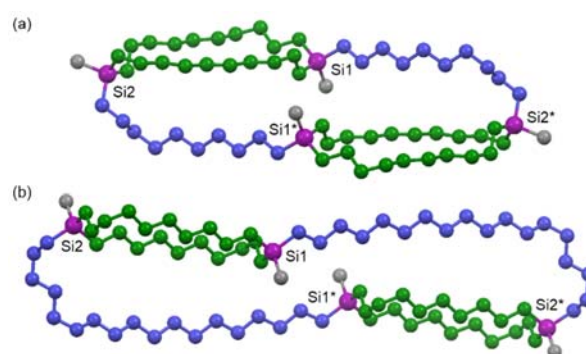
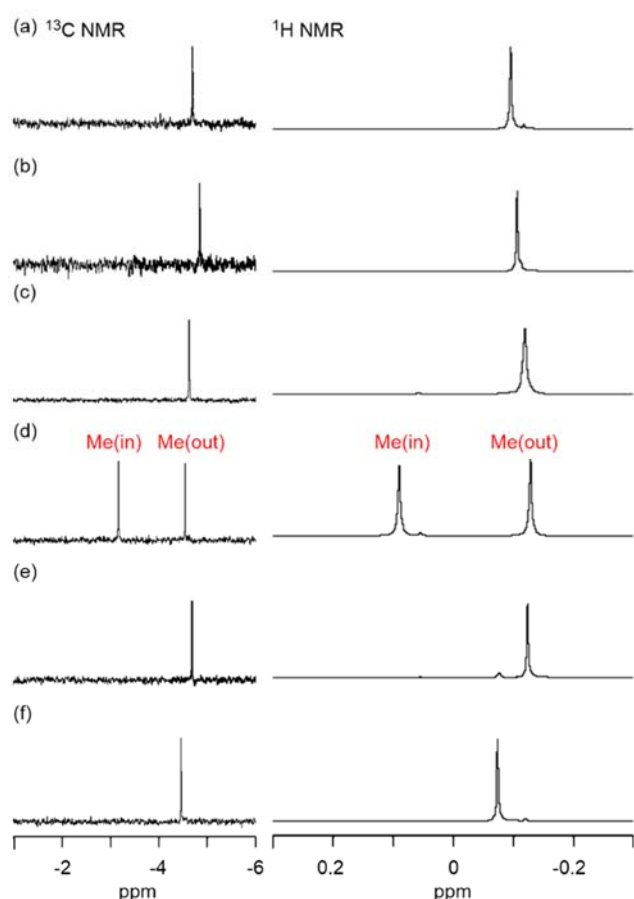


Fig. 3. Molecular structures of tricycloalkanes as determined by X-ray crystallography. Hydrogen atoms were omitted for clarity: (a) **2a** and (b) **2b**.

Further recycling of the bicycloalkane portion (Fraction C) in the GPC (Fig. 2b) resulted in two distinct peaks. The fraction with the shorter retention time was named C1, and the latter one was named C2. In the reaction of **4b**, fractions C1 and C2 contained pure *syn*-**1a**<sup>3</sup> and *anti*-**1a**<sup>3</sup>, respectively, of which NMR spectra (Fig. 4cd) and GPC retention times for these fractions were completely identical to those reported previously.<sup>3</sup>

Since bicyclo[18.10.10]alkanes **1b** with one differing alkyl side chain were obtained in an oily form, their molecular structures could not be determined by X-ray crystallography. Therefore, their most stable forms in solution were identified by comparing NMR spectra with those of previously reported related compounds. It is generally accepted that the stable forms of flexible bicycloalkanes can be plausibly identified by referring to the symmetry of the signals and the chemical shifts of substituents.<sup>1</sup>

The <sup>13</sup>C NMR spectrum of *syn-1b* exhibits C<sub>2v</sub> symmetry, indicating that the stable form is either out,out-, in,in-, or their interchange. Compared with the spectrum of the in,out-form of *anti-1a*<sup>3</sup> (Fig. 4d), which shows in-Me ( $\delta_{\text{C}} -3.2^1$ ) and out-Me ( $\delta_{\text{C}} -4.6^1$ ) signals in CDCl<sub>3</sub>, the chemical shift of the methyl signal in *syn-1b* ( $\delta_{\text{C}} -4.7$  (Fig. 4e)) is closer to that of out-Me of *anti-1a*. Additionally, five CH<sub>2</sub> and seven CH<sub>2</sub> signals with a 2:1 intensity ratio were observed; the former signals are assignable to two equivalent C10-side chains, and the latter to one C18-chain. Therefore, the spectrum of *syn-1b* is plausibly assignable to the out,out-form. Temperature-dependent <sup>13</sup>C NMR of *syn-1b* was investigated (Fig. S27), however, no significant changes in the spectra were observed.



**Fig. 4.** <sup>13</sup>C (left) and <sup>1</sup>H (right) NMR methyl signals of bicycloalkanes and tricycloalkanes in CDCl<sub>3</sub> at 298 K: (a) **2a**; (b) **2b**; (c) *syn-1a*<sup>1,3</sup>; (d) *anti-1a*<sup>1,3</sup>; (e) *syn-1b*; (f) *anti-1b*.

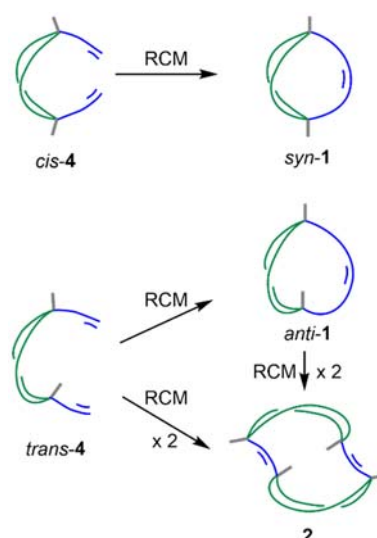
The <sup>1</sup>H NMR spectrum of *syn-1b* also supports the out,out-form, as the chemical shift of Me ( $\delta_{\text{H}} -0.13$  (Fig. 4e)) aligns with

that of out-Me ( $\delta_{\text{H}} -0.13^1$ ) rather than in-Me ( $\delta_{\text{H}} 0.07^1$ ) from the in,out-form of *anti-1a* (Fig. 4d). Temperature-dependent <sup>1</sup>H NMR of *syn-1b* also showed no significant changes in the spectra (Fig. S28).

Unexpectedly, the <sup>1</sup>H and <sup>13</sup>C NMR spectra of *anti-1b* showed an equivalent methyl signal (Fig. 4f), which is different from *anti-1a*<sup>1,3</sup> (Fig. 4d) that exhibits inequivalent Me signals due to its in,out-form. The signal of *anti-1b* attributed to either the stable crossed-out,out-form with the crossing C18-chain or a facile exchanging in,out-form. To analyse dynamic behaviour of *anti-1b*, the <sup>1</sup>H and <sup>13</sup>C NMR spectrum of *anti-1b* was recorded at low temperature (210 K) (Fig. S29 (<sup>13</sup>C) and S30 (<sup>1</sup>H)). However, the details could not be elucidated due to almost no change in the signals.

The formation mechanism for BCAs and TCAs is discussed (Fig. 5). Intramolecular RCM of *cis-4* and *trans-4* can afford *syn-1* and *anti-1*, respectively. Despite adopting dilution conditions for the RCM reaction, the TCA **2**, a dimeric compound of the bicycloalkanes, were obtained in good yield. Several diastereomers of tricycloalkanes can be formed by dimerization of two alkenylcycloalkanes and/or two bicycloalkanes, the observed diastereomer of tricycloalkane shown in Fig. 3 in this study was produced by head-to-tail coupling of two *trans-4* or two *anti-1*. Although *cis-4* can also plausibly undergo dimerization, its dimerization products were not observed due to the low yield of *cis-4* in the reaction.

The isolated yields of the products are summarized in Table 1. These results reflect the equilibrium of the RCM reaction<sup>4</sup> due to the long reaction time (2 days). High yields of *anti*-BCA and its dimeric TCA, which can be formed from *trans-4*, were observed, although the exact *cis/trans* ratio of reactant **4** could not be determined as already described. These results suggest that *trans-4* is likely the dominant component in the *cis/trans*-mixture of reactants in these studies, which is consistent with the use of the *trans*-rich precursor **3**.



**Fig. 5.** Formation mechanism for bicycloalkanes (*syn/anti-1*) and the isolated tricycloalkane **2** by ring-closing metathesis (RCM) reaction of dialkenyldisilacycloalkane (*cis/trans-4*).

## Conclusions

A simultaneous synthesis of two diastereomers of disilabicycloalkanes was demonstrated through the RCM reaction of *cis*- and *trans*-dialkenyldisilacycloalkanes, followed by hydrogenation. Additionally, a dimeric compound, specifically a tricycloalkane, was also generated in each reaction and characterized. This method allows for the synthesis of bicycloalkanes in which the lengths of one of the three bridging chains connecting the two bridgeheads differ from the others. In fact, two diastereomers of dimethylbicyclo[18.10.10]alkanes, namely *syn*- and *anti*-bicycloalkanes, were obtained, both in oily form.

The most stable form of each bicycloalkane in solution was analysed using NMR spectra, although complete identification remains challenging due to their flexible skeletons. The spectra of *syn*-**1b** are plausibly assigned to the out,out-form, consistent with that observed for *syn*-**1a**<sup>1,3</sup>. The spectra of *anti*-**1b** suggest assignment to the crossed-out,out-form which features the longest C18 crossing chain or an exchanging in,out-form, although the spectrum of *anti*-**1a**<sup>1,3</sup> is indicative of an in,out-form.

The observed symmetries of the NMR spectra of *anti*-bicyclo[n.10.10]alkanes (*n* = 10 and 18) depend significantly on the length of the side chain. This is noteworthy because it is the first time the effect of side chain length perturbation on the structure in bicycloalkanes has been elucidated. A longer or differing side chain tends to stabilize the crossing structure. These findings may contribute to the molecular design of functional bicycloalkanes based on structural transformations of the stable forms.

## Author Contributions

The project was designed by WS. Synthetic studies were conducted by YT. NMR and X-ray experiments and the data analysis were carried out by YT and YI. HRMS measured by KY and KO. WS and YT wrote paper. All authors have approved the final version of the manuscript.

## Data availability

Data for this article, including synthetic details, copies of NMR and HRMS spectra, and GPC charts, are available as ESI.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by a JSPS Grant-in-Aid for Scientific Research (B) (JP23H02039 and JP23K26732) and JST the establishment of university fellowships towards the creation of science technology innovation, Grant Number (JPMJFS2139).

## Notes and references

- 1 W. Setaka, *Eur. J. Org. Chem.*, 2024, **27**, e202400206.
- 2 R. W. Alder and S. P. East, *Chem. Rev.*, 1996, **96**, 2097–2111.
- 3 W. Setaka, Y. Ikeda, Y. Inagaki, K. Ohara and K. Yamaguchi, *Org. Lett.* 2023, **25**, 7283–7286.
- 4 (a) R. Tuba and R. H. Grubbs, *Polym. Chem.*, 2013, **4**, 3959–3962; (b) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746; (c) R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2006, **45**, 3760; (d) R. H. Grubbs, in *Handbook of metathesis*, ed. R. H. Grubbs, Wiley-VCH, Weinheim, 2003, vol. 1–3; (e) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
- 5 I. W. Jones, Y. Monguchi, A. Dawson, M. D. Carducci and E. A. Mash, *Org. Lett.*, 2005, **7**, 2841–2843.
- 6 (a) W. Setaka, S. Higa and K. Yamaguchi, *Org. Biomol. Chem.*, 2014, **12**, 3354–3357. (b) Y. Ikeda, Y. Inagaki and W. Setaka, *Chem. Commun.*, 2021, **57**, 7838–7841.
- 7 (a) S. T. Phan, W. Setaka and M. Kira, *Chem. Lett.* **2008**, 37, 976–977. (b) S. T. Phan, W. Setaka and M. Kira, *Chem. Lett.* **2007**, 36, 1180–1181.
- 8 S. R. Zarccone, N. Bhuvanesh and J. A. Gladysz, *Chem. Eur. J.*, 2023, **29**, e202302200.
- 9 Y. Zhu, M. Stollenz, S. R. Zarccone, S. Kharel, H. Joshi, N. Bhuvanesh, J. H. Reibenspies and J. A. Gladysz, *Chem. Sci.*, 2022, **13**, 13368–13386.
- 10 A. L. Estrada, L. Wang, G. Hess, F. Hampel and J. A. Gladysz, *Inorg. Chem.*, 2022, **61**, 17012–17025.
- 11 S. Kharel, T. Jia, N. Bhuvanesh, J. H. Reibenspies, J. Blemel and J. A. Gladysz, *Chem. Asian J.*, 2018, **13**, 2632–2640.
- 12 M. Stollenz, D. Taher, N. Bhuvanesh, J. H. Reibenspies, Z. Baranov and J. A. Gladysz, *Chem. Commun.*, 2015, **51**, 16053–16056.
- 13 M. Stollenz, M. Barbasiewicz, A. J. Nawara-Hultzs, T. Fiedler, R. M. Laddusaw, N. Bhuvanesh and J. A. Gladysz, *Angew. Chem. Int. Ed.*, 2011, **50**, 6647–6651.
- 14 S. R. Zarccone, P. J. Verardi, N. Bhuvanesh and J. A. Gladysz, *Chem. Commun.*, 2022, **58**, 8694.
- 15 (a) Y. Tu, Y. Inagaki and W. Setaka, *J. Org. Chem.*, 2024, **89**, 6222–6229; (b) Y. Tu, Y. Inagaki, E. Kwon and W. Setaka, *Chem. Lett.*, 2021, **50**, 1397–1399.

**Data availability**

Data for this article, including synthetic details, copies of NMR and HRMS spectra, and GPC charts, are available as ESI.