Organic LETTERS

Letter

pubs.acs.org/OrgLett

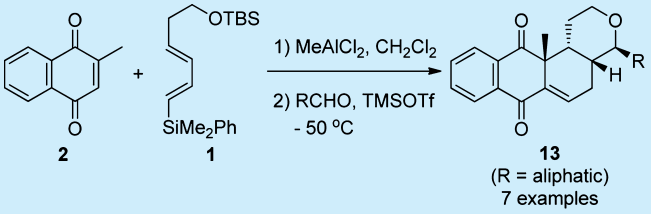
Synthesis of Isochromene-Type Scaffolds via Single-Flask Diels–Alder-[4 + 2]-Annulation Sequence of a Silyl-Substituted Diene with Menadione

Jihoon Lee and James S. Panek*

Department of Chemistry and Center for Chemical Methodology and Library Development, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: A sequential Diels–Alder reaction/silicon-directed [4 + 2]-annulation was developed to assemble hydroisochromene-type ring systems from menadione **2**. In the first step, a Diels–Alder of the 1-silyl-substituted butadiene **1** with **2** furnished an intermediate cyclic allylsilane. Subsequently, TMSOTf promoted a [4 + 2]-annulation through trapping of an oxonium, generated by condensation between an aldehyde and the TBS protected alcohol resulted in the formation of a *cis*-fused hydroisochromene **13**.



Substituted isochromene (2-benzopyran) frameworks are frequently found in many natural products and bioactive molecules.[1] This class of molecules has inspired the development of efficient synthetic methods for various isochromene-type ring systems, and as a result, several useful methods have been developed. The majority relies on an activation of alkyne or olefin and subsequent addition of an oxygen atom.[2] However, the efficient stereocontrolled synthesis of a fused cyclic hydroisochromene skeleton still remains a useful objective.[3] Development of reaction processes that provide access to heteroatom-bearing polycyclic scaffolds (isochromene-like) would be a useful contribution to the field. Furthermore, application of a divergent cyclization method to diversity-oriented synthesis (DOS) would allow for a useful method to establish novel and stereochemically well-defined ring systems.

Recently we reported a synthesis of hydrobenzofurans using transannular cyclization of a tethered allylsilane, which was rapidly prepared through an alkyne–alkyne reductive coupling between a propargylsilane and terminal hydroxy-bearing olefin.[4] Therein, we demonstrated that the tethered allylsilanes participate in annulations, leading to the formation of *trans*-fused hydrobenzofurans. Since allylsilanes have been shown to be useful reaction partners in annulation reactions,[5] allylsilanes possessing a higher degree of structural complexity would also be useful substrates in the construction of fused cyclic systems by a silicon-directed annulation. Herein, we describe our studies aimed at the development of a cascade cyclization utilizing an organosilane compound to furnish a hydroisochromene scaffold.

In that regard, the use of a Diels–Alder reaction of a 1,4-substituted butadiene with a paranaphthoquinone (Figure 1) would afford a linear fused-tricyclic ring system bearing a stereochemically well-defined allylsilane embedded in the *cis*-fused decalin. In the subsequent step, the resulting carbon nucleophile will participate in a silicon-directed annulation in the presence of an aldehyde to construct tetracyclic compound **6**.

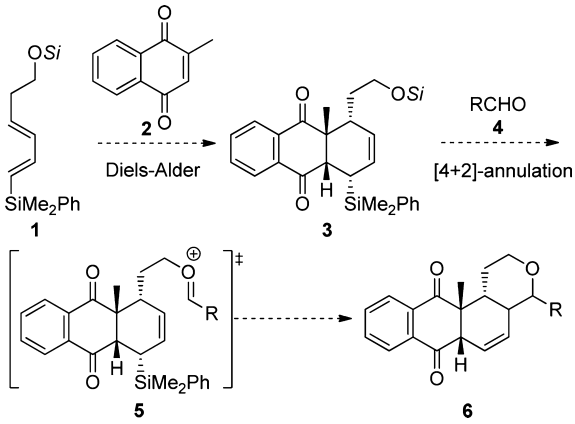


Figure 1. Proposed tandem Diels–Alder/annulation sequence.

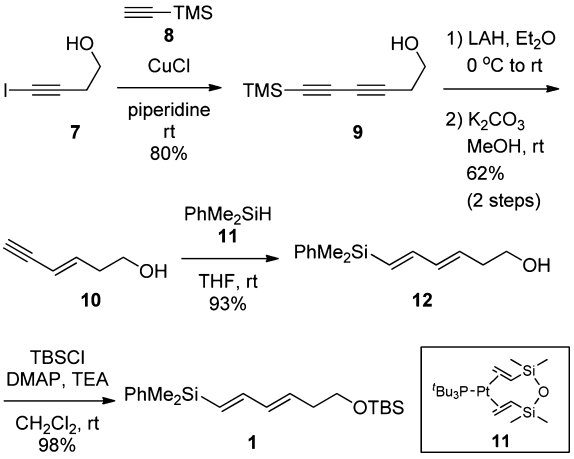
A similar idea had been previously employed in the tendem processes, where polycyclic systems were successfully produced through the reaction sequences involving Diels–Alder/Schmidt,[6] Diels–Alder/allylation,[7] and IMDA/[3 + 2]-annulation.[8] Accordingly, we envisioned that a one-pot Diels–Alder/[4 + 2]-annulation sequence would result in a stereoselective approach to complex polycyclic scaffolds.

The development of this sequence began by establishing an efficient and scalable synthesis of silicon-substituted 1,3-diene **1** (Scheme 1). Thus, 1-iodobutynol **7**[9] underwent a copper-

Received: May 8, 2014
Published: June 11, 2014

   dx.doi.org/10.1021/ol501329t | *Org. Lett.* 2014, 16, 3320–3323

Scheme 1. Preparation of Silicon-Substituted Diene 1

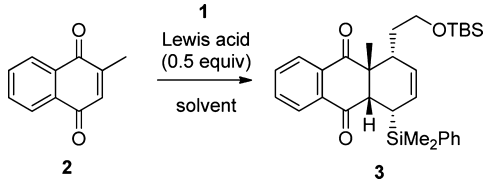


mediated coupling with TMS-acetylene **8** to produce diyne **9**.[10] Selective reduction of the homopropargylic alkyne to an (*E*)-alkene using $LiAlH_4$ was followed by protodesilylation of the resulting enyne without purification to provide **10** in 62% yield.[11] Regioselective hydrosilylation of **10** was conducted utilizing [Pt(DVDS)]-P^{t}Bu$_3$ (Chandra's catalyst[12]) **11** to afford silane-substituted diene **12** in 93% yield as a single regioisomer.[13]

At that point, it seemed that the selection of a proper protecting group for the hydroxy group in **12** would be crucial for a successful annulation reaction,[14] as it has to be spontaneously removed after the Diels–Alder reaction to generate an oxocarbenium ion with an aldehyde under the given reaction conditions. In our earlier three-component propargylation reaction utilizing allenylsilanes,[15] the TBS ether successfully participated in the formation of an oxonium ion with an aldehyde promoted by TMSOTf. In our initial study, therefore, TBS was determined to be the protecting group for the terminal hydroxy group to afford diene **1**.

An initial Lewis acid screening determined that bidentate aluminum-based promoters[16] efficiently affected the reaction to give **3** in a useful yield and as a single regioisomer (Table 1).[17] A series of reactions using other Lewis acids [BF_3·OEt_2, $TiCl_4$, and Cu(OTf)$_2$] provided inferior results in terms of reaction efficiency, while thermal conditions in refluxing benzene without Lewis acid activation gave no reaction. Unfortunately,

Table 1. Diels–Alder Reactions of Diene 1 with Dienophiles 2



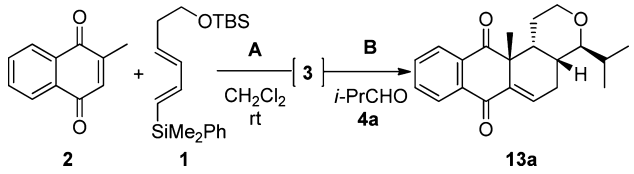
entry[a]	LA	solvent	temp (°C)	yield (%)[b]
1	none	benzene	80	nr
2	Me_2AlCl	CH_2Cl_2	25	ta
3	$MeAlCl_2$	CH_2Cl_2	25	77
4	$AlCl_3$	CH_2Cl_2	25	60

[a]The reactions were conducted under 0.2 M concentration of **1**. [b]Purification yield after column chromatography on SiO_2. nr = no reaction; ta = trace amount.

we were unable to find an optimal condition for the DA reaction using other types of dienes and dienophiles. For example, the reactions using 2-ethyl substituted naphthoqinone or cyclohexenone gave a low conversion or trace amount of product, respectively.

As such, we pursued a silicon-directed annulation to access a stereochemically well-defined hydroisochromene skeleton and explored the possibility of a one-pot Diels–Alder/annulation. In these experiments, the reaction between **1** and **2** was conducted prior to addition of aldehyde **4a** to secure the formation of allylsilane **3**. After extensive screening of reaction conditions, we learned that TMSOTf (2.0 equiv) was effective in promoting the annulation with an aldehyde at −50 °C to afford the fused pyran **13a**, which was generated through migration of the double bond in **6** into conjugation with the carbonyl [66% yield as a single diastereomer (Table 2)].

Table 2. Optimization of One-Pot Sequential Diels–Alder/Annulation



entry[a]	A[b]	B (equiv)	temp (°C)	yield (%)[c]
1	$AlCl_3$	–	0 to 25	–
2	$AlCl_3$	BF_3·OEt_2 (1.2)	−78 to 25	17
3	$AlCl_3$	$TiCl_4$ (1.0)	−78 to 25	ta
4	$AlCl_3$	ln(OTf)$_3$ (1.0)	0 to 25	17
5	$AlCl_3$	TMSOTf (2.0)	−50	40
6	$MeAlCl_2$	TMSOTf (2.0)	−50	66

[a]The reactions were conducted at 0.2 M concentration of **1** in CH_2Cl_2. [b]0.5 equiv of Lewis acid was used. [c]Purification yield after column chromatography on SiO_2. ta = trace amount.

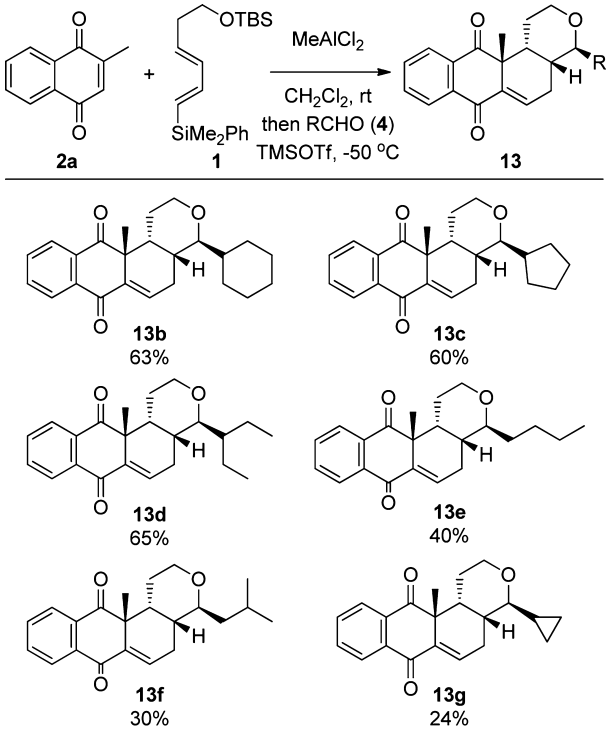
The scope of the process was evaluated with a range of aldehydes, while employing the optimized conditions. The DA was carried out in the presence of $MeAlCl_2$, and aldehyde **4** and TMSOTf were subsequently added to the reaction mixture at −50 °C to furnish the desired fused-cyclic compounds (Scheme 2). The sequence using aldehydes **4b** and **4c** showed similar reactivity to the reaction of isobutylaldehyde **4a** and resulted in the formation of products **13b** and **13c** in 63% and 60% yield, respectively, as a single diastereomer. Also, 2-ethylbutyrl-aldehyde proved to be a good reaction partner in this reaction sequence, which gave **13d** in 65% yield. Given the observed results from the reaction of **4a**, **4b**, **4c**, and **4d**, it was concluded that *α*-branched aldehydes served as excellent reaction partners in this annulation sequence.

Additionally, valeraldehyde **4e**, a linear aldehyde, gave the desired cyclic compound **13e** in 40% yield. The effect of *β*-branching on the annulations was also examined using isovaleraldehyde **4f**. However, this trial provided **13f** in 30% yield albeit as a single diastereomer. In addition, the reaction of cyclopropanecarboxaldehyde **4g** proceeded with unidentified side reactions and gave the product **13g** in only 24% yield. Utilization of aromatic aldehydes under the optimal reaction conditions provided a mixture of unidentified reaction products.

Through the extensive experiments to elucidate the scope of this reaction sequence, it was turned out that the 2-alkyl

dx.doi.org/10.1021/ol501329t | Org. Lett. 2014, 16, 3320–3323

Scheme 2. One-Pot Diels–Alder-Annulation Sequence with Various Aldehydes (4b–4g)[a]



[a]Isolated yield after purification by SiO_2 chromatography.

substituent on naphthoquinone is crucial in a successful annulation reaction.[18] The DA reaction using naphthoquione as the diene part proceeded to form an adduct in 73% yield, but formation of the desired isochromene-type scaffold was not observed in the subsequent annulation step. Although the DA/annulation sequence exhibits limitations in reaction scope, this strategy assembles a high degree of complexity through simple manipulations with various aliphatic aldehydes, which allows for rapid establishment of a focused chemical library.

The stereochemical outcome[19] of the Diels–Alder/annulation sequence was particularly interesting, where an initial Prins-type cyclization proceeds through a chair-boat-like transition state **T1** (Figure 2),[20] positioning the bulky silicon

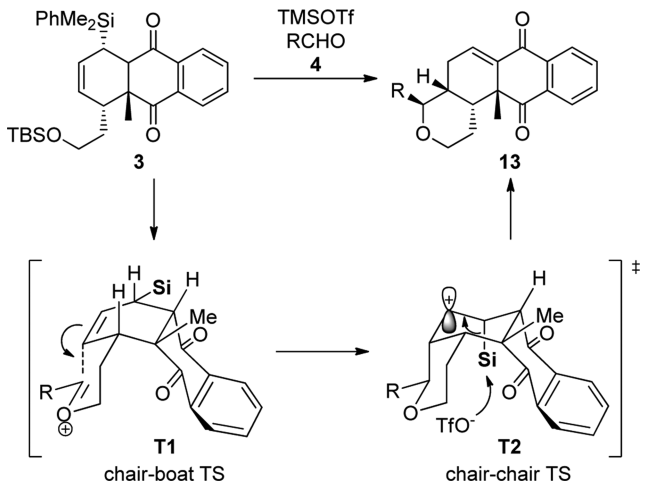


Figure 2. Proposed transition state of [4 + 2]-annulations.

group in a pseudoequatorial orientation to help minimize destabilizing 1,3-diaxial interactions that would develop in a chair–chair conformation. Subsequent boat to chair interconversion then aligns the C–Si σ-bond with the empty p-orbital (**T2**) that maximizes the electron-donating effect of the silyl group (β-silicon effect). Elimination of the silicon group followed by isomerization of the double bond into conjugation gave the *cis*-fused cyclic compound **13**.

We have described a one-pot sequential Diels–Alder/annulation sequence employing a silyl-substituted diene that rapidly assembles a complex tetracyclic scaffold bearing a *cis*-fused hydroisochromene. Experiments aimed at the development of an asymmetric variant will allow access to enantioenriched fused-cyclic scaffolds, and studies to broaden the reaction scope will be the focus of future studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for new compounds **1**–**13g** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: panek@bu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the NIGMS CMLD initiative (P50-GM067041). We are grateful to Dr. Paul Ralifo, Dr. Norman Lee, and Dr. Jeffrey Bacon (Chemical Instrumentation Center at Boston University) for helpful discussions and assistance with NMR, HRMS, and X-ray crystallographic analysis experiments.

■ REFERENCES

(1) For ventiloquinones, see: (a) Hanumaiah, T.; Marshall, D. S.; Rao, B. K.; Rao, C. P.; Rao, G. S. R.; Rao, J. U. M.; Rao, K. V. L; Thomson, R. H. *Phytochemistry* **1985**, *24*, 2373–2378. (b) Jammula, S. R.; Papalla, S. B.; Telikepalli, H.; Rao, K. V. J.; Thomson, R. H. *Phytochemistry* **1991**, *30*, 3741–3744. (c) Ali, S.; Read, R. W.; Sotheeswaran, S. *Phytochemistry* **1994**, *35*, 1029–1032. (d) Brimble, M. A.; Dancalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267–281. For other examples of natural products and bioactive molecules, see (e) Hayashi, T.; Smith, F. T.; Lee, K.-H. *J. Med. Chem.* **1987**, *30*, 2005–2008. (f) Abas, F.; Lajis, N. H.; Shaari, K.; Israf, D. A.; Stanslas, J.; Yusuf, U. K.; Raof, S. M. *J. Nat. Prod.* **2005**, *68*, 1090–1093. (g) Shishido, Y.; Wakabayashi, H.; Koike, H.; Ueno, N.; Nukui, S.; Yamagishi, T.; Murata, Y.; Naganeo, F.; Mizutani, M.; Shimada, K.; Fujiwara, Y.; Sakakibara, A.; Suga, O.; Kusano, R.; Ueda, S.; Kanai, Y.; Tsuchiya, M.; Satake, K. *Bioorg. Med. Chem.* **2008**, *16*, 7193–7205. (h) Kuo, Y.-J.; Hsiao, P.-C.; Zhang, L.-J.; Wu, M.-D.; Liang, Y.-H.; Ho, H.-O.; Kuo, Y.-H. *J. Nat. Prod.* **2009**, *72*, 1097–1101.

(2) (a) Butin, A. V.; Abaev, V. T.; Mel'chin, V. V.; Dmitriev, A. S. *Tetrahedron Lett.* **2005**, *46*, 8439–8441. (b) Villeneuve, K.; Tam, W. *Eur. J. Org. Chem.* **2006**, 5449–5453. (c) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462–4468. (d) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 9548–9551. (e) Murai, M.; Uenishi, J.; Uemura, M. *Org. Lett.* **2010**, *12*, 4788–4791. (f) Murai, M.; Sota, Y.; Onohara, Y.; Uenishi, J.; Uemura, M. *J. Org. Chem.* **2013**, *78*, 10986–10995. (g) Malhotra, D.; Liu, L.-P.; Mashuta, M. S.; Hammond, G. B. *Chem.—Eur. J.* **2013**, *19*, 4043–4050. (h) Saito, K.; Kajiwara, Y.;

Akiyama, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 13284−13288. (i) Cui, Y.; Villafane, L. A.; Clausen, D. J.; Floreancig, P. E. *Tetrahedron* **2013**, *69*, 7618−7626.
(3) (a) Yadav, J. S.; Reddy, B. V. S.; Ganesh, A. V.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2010**, *51*, 2963−2966. (b) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Grée, R. *J. Org. Chem.* **2011**, *76*, 7677−7690. (c) Reddy, B. V. S.; Kumar, H.; Borkar, P.; Yadav, J. S.; Sridhar, B. *Eur. J. Org. Chem.* **2013**, 1993−1999.
(4) Wu, J.; Pu, Y.; Panek, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 18440−18446.
(5) (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836−9837. (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231−3234.
(6) (a) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018−6024. (b) Frankowski, K. J.; Neuenswander, B.; Aubé, J. *J. Comb. Chem.* **2008**, 721−725. (c) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712−15713. (d) Zeng, Y.; Reddy, S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993−4995.
(7) (a) Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254−5266. (b) Organ, M. G.; Winkle, D. D. *J. Org. Chem.* **1997**, *62*, 1881−1885.
(8) Elliott, G. I.; Fuchs, J. R.; Blagg, B. S. J.; Ishikawa, H.; Tao, H.; Yuan, Z.-Q.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10589−10595.
(9) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E. *J. Am. Chem. Soc.* **2001**, *123*, 3194−3204.
(10) (a) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841−6844. (b) Danilkina, N.; Nieger, M.; Selivanov, S.; Bräse, S.; Balova, I. *Eur. J. Org. Chem.* **2012**, 5660−5664.
(11) Smith, A. B.; Dong, S.; Fox, R. J.; Brenneman, J. B.; Vanecko, J. A.; Maegawa, T. *Tetrahedron* **2011**, *67*, 9809−9828.
(12) Chandra, G.; Lo, P. Y.; Hitchcock, P. B.; Lappert, M. F. *Organometallics* **1987**, *6*, 191−192.
(13) Bergueiro, J.; Montenegro, J.; Cambeiro, F.; Saá, C.; López, S. *Chem.—Eur. J.* **2012**, *18*, 4401−4410.
(14) Bendiabdellah, Y.; Villanueva-Margalef, I.; Misale, A.; Nahar, K. S.; Haque, M. R.; Thurston, D. E.; Zinzalla, G. *Synthesis* **2011**, 2321−2333.
(15) Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett.* **2010**, *12*, 336−339.
(16) Hilt, G.; Pünner, F.; Möbus, J.; Naseri, V.; Bohn, M. A. *Eur. J. Org. Chem.* **2011**, 5962−5966.
(17) (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092−4094. (b) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415−2434.
(18) The reaction of a naphthoquinone bearing a methyl carboxylate at the 2-position under the optimal conditions (**1** and **3a**) also afforded a desired product, albeit in a low yield (∼10%).
(19) For the X-ray crystallographic analysis, see the Supporting Information.
(20) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425−2430.