

Synthesis of Cyclohexanes via [3 + 3] Hexannulation of Cyclopropanes and 2-Chloromethyl Allylsilanes

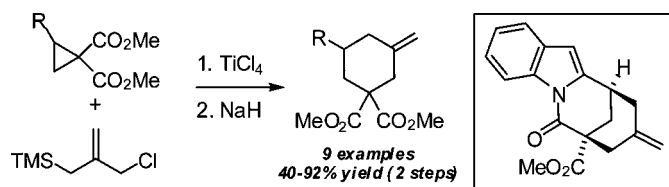
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ABSTRACT



Lewis acid-assisted ring-opening/allylation of 1,1-cyclopropane diesters, followed by base-mediated ring closure, generates functionalized *exo*-methylenecyclohexanes in good yield. This two-step procedure is highlighted by expedient preparation of a pyrido[1,2-*a*]indole skeleton common to the chippine class of *iboga* indole alkaloids.

Since their first introduction by Trost and Chan,¹ Pd-trimethylenemethane (Pd-TMM) complexes (or their synthetic equivalents)² have proven to be versatile three-carbon synthons in [3 + 2] cycloadditions with electron-deficient olefins³ en route to functionalized cyclopentanes (Figure 1, eq 1); more recent reports have described cycloadditions with imines,⁴ and in a [3 + 3] sense, with aziridines,⁵ azomethine imines,⁶ and nitrones.⁷ Such reaction diversity serves to demonstrate the utility of these all-carbon dipole equivalents in preparation of a broad array of carbo- and heterocycles.

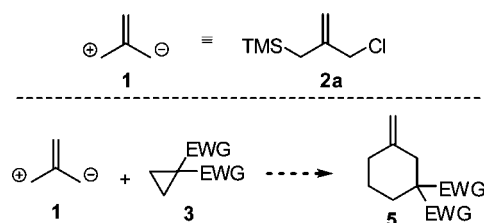


Figure 1. Reaction of 1,1-cyclopropane diesters with a TMM equivalent.

The reagent 2-(chloromethyl)-3-trimethylsilyl-1-propene **2a** can be considered a synthetic equivalent of TMM zwitterion **1** (Figure 1). This bifunctional reagent has found use in [3 + 2] annulations for introduction of the exomethylenic substituent by way of sequential allylation/annulation reactions.⁸ In our ongoing research program concerning the reactivity of donor–acceptor (D–A) cyclopropanes, we were curious if an all-carbon dipole could be used in the context of a [3 + 3] annulation⁹ to achieve the synthesis of functionalized cyclohexane rings.

(1) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.

(2) For a review of Pd-TMM cycloadditions see: (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1.

(3) For an asymmetric variant, see: Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328, and references therein.

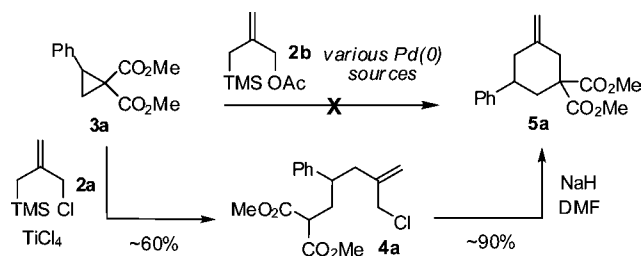
(4) (a) Yamago, S.; Nakamura, M.; Wang, X.-Q.; Yanagawa, M.; Tokumitsu, S.; Nakamura, E. *J. Org. Chem.* **1998**, *63*, 1694. (b) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 12398.

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(6) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330.

(7) Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5901.

Scheme 1. Investigation of Cyclization Conditions



Herein we describe a stepwise, formal [3 + 3] annulation reaction of substituted 1,1-cyclopropane diesters with a TMM equivalent, to provide *exo*-methylenecyclohexanes. In addition, we describe its application to the rapid synthesis of a pyrido[1,2-*a*]indole skeleton common to a subclass of *Iboga* indole-containing natural products.

We began with a search for suitable cycloaddition conditions using 2-phenyl-1,1-cyclopropanediester **3a** (Scheme 1). Conditions known to effect the cycloaddition of TMM precursor **2b** onto electron deficient olefins failed to provide cycloadduct when using cyclopropane **3a**. Altering the strategy slightly, the cyclopropane **3a** was treated with the chormethylallylsilane **2a** under the influence of TiCl_4 resulting in smooth allylation. The usefulness of such an intermediate was not lost on us; a simple intramolecular $\text{S}_{\text{N}}2$ reaction of **4a** with a malonate anion would also provide the target cyclohexanes; indeed, treatment of **4a** with NaH gave cyclohexane **5a** in excellent yield. Of a brief survey of common Lewis acids (including $\text{Yb}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, $\text{BF}_3\cdot\text{OEt}_2$, MgI_2 , AgOTf , SnCl_4 , EtAlCl_2^{10}), TiCl_4^{11} was found to provide the highest yields and cleanest reactivity profiles for ring-opening. A screening of numerous additives (organic/inorganic bases, Ag(I) sources) was carried out to effect a one-pot cyclization, however with no success. Variation of leaving group (I, OTs) also failed to achieve *in situ* ring closure.

The scope of the allylation/ring closure protocol was investigated (Table 1). A number of items are to be noted. At present, we are limited to the use of aromatic, heteroaromatic,

Table 1. Substrate Scope of a Stepwise Annulation of 1,1-Cyclopropane Diesters

entry	cyclopropane (3)	allylation product (4)	cyclohexene (5)
1	3a $\text{R}^1 = \text{Phenyl}$ $\text{R}^2 = \text{H}$	4a : 92%	5a : 95%
2	3b $\text{R}^1 = 4\text{-BrC}_6\text{H}_4$ $\text{R}^2 = \text{H}$	4b : 88%	5b : 95%
3	3c $\text{R}^1 = 2\text{-piperonyl}$ $\text{R}^2 = \text{H}$	4c : 74%	5c : 97%
4	3d $\text{R}^1 = 1\text{-naphthyl}$ $\text{R}^2 = \text{H}$	4d : 88%	5d : 91%
5	3e $\text{R}^1 = 2\text{-thienyl}$ $\text{R}^2 = \text{H}$	4e : 62%	5e : 90%
6	3f $\text{R}^1 = 4\text{-indolyl}$ $\text{R}^2 = \text{H}$	4f : 81%	5f : 91%
7	3g $\text{R}^1 = \text{Vinyl}$ $\text{R}^2 = \text{H}$	4g : 83%	5g : 79%
8	3h $\text{R}^1, \text{R}^2 = \text{cyclohexyl}$	4h	5h : 75%
		6 72% (2:1 4h : 6) (as inseparable mixture)	

^a **2a** (1.2 equiv), TiCl_4 (1.0 M CH_2Cl_2 , 1.0 equiv), CH_2Cl_2 /−78 °C ^b NaH (1.1 equiv), DMF/ 0 °C

(8) (a) Boto, A.; Hernández, D.; Hernández, R.; Montoya, A.; Suárez, E. *Eur. J. Org. Chem.* **2007**, 325. (b) Sadakane, M.; Vahle, R.; Schierle, K.; Kolter, D.; Steckhan, E. *Synlett* **1997**, 95. (c) D'Aniello, F.; Mattii, D.; Taddei, M. *Synlett* **1993**, 119. (d) Guiles, J. W.; Meyers, A. I. *J. Org. Chem.* **1991**, 56, 6873. (e) Knapp, S.; O'Connor, U.; Mobilio, D. *Tetrahedron Lett.* **1980**, 21, 4557.

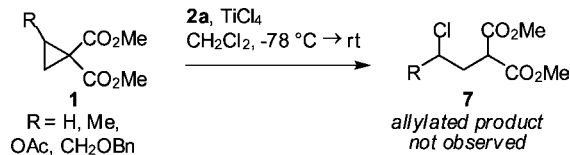
(9) Formal [3 + 3] annulations of 1,1-cyclopropane diesters and azomethine imines: Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, 10, 689. Formal [3 + 3] annulations of 1,1-cyclopropane diesters and nitrones: (a) Carson, C. A.; Young, I. S.; Kerr, M. A. *Synthesis* **2008**, 485. (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, 72, 10251. (c) Sapeta, K.; Kerr, M. A. *J. Org. Chem.* **2007**, 72, 8597. (d) Kang, Y.-B.; Sun, X. L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, 46, 3918. (e) Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, 127, 5764. (f) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, 42, 3023.

(10) EtAlCl_2 has been used to allylate D-A cyclopropanes: Bambal, R. Kemmitt, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734. We chose TiCl_4 for cleanliness of the reaction and faster reaction times.

(11) For TiCl_4 -mediated allylations of D-A cyclopropanes, see: (a) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, 5, 4639. (b) Sugita, Y.; Yamadoi, S.; Hosoya, H.; Yokoe, I. *Chem. Pharm. Bull.* **2001**, 49, 657.

matic, vinylic and spiro-fused cyclopropanes. Reactivity is presumably dependent on stability of a putative ring-opened intermediate; cyclopropanes capable of supporting benzylic,

Scheme 2



allylic and 3° carbocations, respectively, are shown to be ideal substrates.

There appears to be minimal reactivity difference between electron-rich (**3c**, entry 3) and electron-poor (**3b**, entry 2) aryl 1,1-cyclopropane diesters. Heteroaromatic systems are well-tolerated (**3e-f**, entries 5–6 respectively), although yields are diminished in the case of 2-thienyl-1,1-cyclopropane diester **3e**, most likely due to its sensitivity to acidic conditions.

Both vinyl (**3g**, entry 7) and spiro-cyclohexyl 1,1-cyclopropane diesters (**3h**, entry 8) are allylated in respectable yields; a byproduct of elimination, **6**, invariably accompanies the formation of **4h** as an inseparable mixture (2:1 **4h**:**6**). A byproduct commonly observed under normal reaction conditions is ring-opened **7** (Scheme 2); this is suppressed considerably by conducting the reaction at lower temperatures (-78°C). In the case of unsubstituted, aliphatic or acetoxy-substituted ($\text{R} = \text{OAc}$) cyclopropanes, this byproduct is obtained exclusively over prolonged reaction times with no indication of desired allylated product being formed by ^1H NMR analysis.

Encouraged by these preliminary results, we were eager to re-examine a synthetic challenge explored previously in our laboratory. As part of our research program directed at the total synthesis of naturally occurring alkaloids, methods for the construction of indole-containing natural products have a central role. Of particular interest to us¹² is a subclass of *Iboga* alkaloids possessing complex molecular architecture in the form of a pyrido[1,2-*a*]indole nucleus with all-carbon quaternary center attachment at the indole 2-position. Two relevant alkaloids, 10,11-demethoxychippine (**8**)¹³ and trioncarpine (**9**)¹⁴ are shown in Figure 2; highlighted are the cyclohexyl motifs accessible from this stepwise annulation protocol. It is foreseen that access to both these alkaloids is possible from an intermediate such as **10** (Figure 2).

The application of the above methodology to the synthesis of a tetracyclic subunit common to these *Iboga* alkaloids is shown in Scheme 3. As a straightforward model system, we envisaged a monosubstituted 2-indolyl cyclopropane diester **3i** (*vide infra*) as the simple reaction partner. Thus, Knoevenagel condensation of *N*-tosyl indole-2-carboxaldehyde **11**¹⁵ and dimethyl malonate, followed by cyclopropanation using the Corey-Chaykovsky protocol¹⁶ furnished cyclopropane

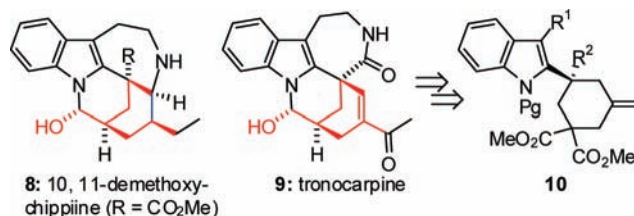
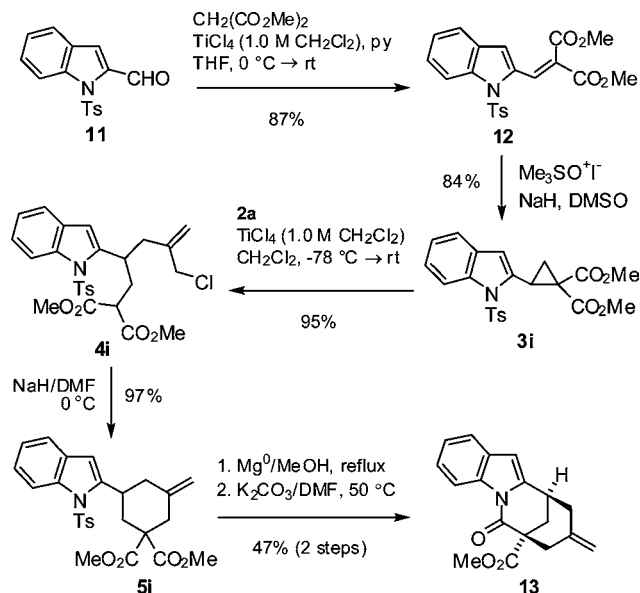


Figure 2. Representative *Iboga* alkaloids of *Tabernaemontana* sp. and possible synthetic precursor **10**.

diester **3i** in excellent yield over the two steps (87%, 84% respectively). Sequential Lewis acid-mediated ring-opening with allylsilane **2a** and treatment with NaH in DMF proceeded gratifyingly to give cyclohexene **5i** in high yield (92% over 2 steps). *N*-Tosyl removal was effected with magnesium metal in methanol, providing the free indole in addition to desired cyclized product **13** in a ratio of 1:3. Subjection of this crude reaction mixture to K_2CO_3 in DMF brought about clean cyclization of the remaining free indole, to pyrido-indole **13** in 47% yield over the two steps. Spatial constraints would dictate the major cyclization product to be that of the reaction of methyl ester *syn* to the pendent 2-indolyl moiety; only one isomer was isolated and the structure verified by 2D-NMR experiments.¹⁷

Scheme 3. Synthesis of Pyrido[1,2-*a*]indole **13**

In summary, we have demonstrated that a stepwise annulation reaction of substituted 1,1-cyclopropane diesters with TMM equivalent **2a** provides *exo*-methylenecyclohexanes in good to excellent yields. Work is ongoing in making this annulation a one-step procedure. Efforts are underway

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(16) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(17) Please see Supporting Information.

to employ this reaction sequence to the preparation of both 10,11-demethoxychippiine (**8**) and tronocarpine (**9**), which will be the topic of further communication.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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