ORGANIC LETTERS

2009
Vol. 11, No. 10
2081−2084

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

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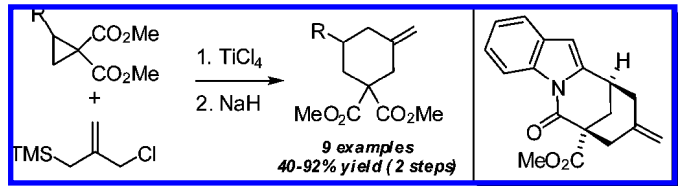
Received March 4, 2009

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 chippiine 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 olefins[3] 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.

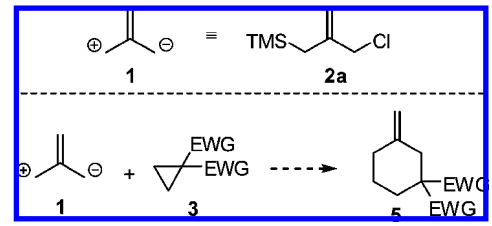


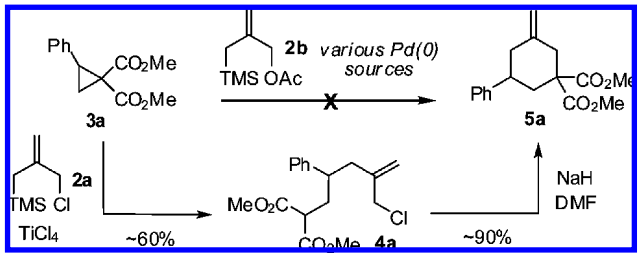
Figure 1. Reaction of 1,1-cyclopropane diesters with a TMM equivalent.

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] annulation[9] 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.
(5) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286. (c) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (d) Mancey, N. C.; Butlin, R. J.; Harrity, J. P. A. *Synlett* **2008**, 2647.
(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**, *4*, 6–5901.

10.1021/ol900457z CCC: $40.75
Published on Web 04/10/2009

Scheme 1. Investigation of Cyclization Conditions

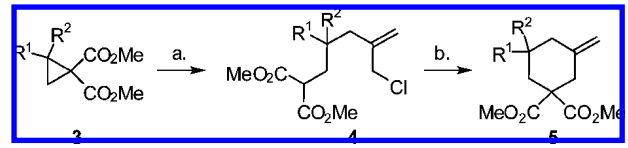


Herein we describe a stepwise, formal [3 + 3] annulation reaction of substituted 1,1-cyclopropane diesters with a TMM equivalent, to provide *exo*-methylenecyclohexanes In addition, we describe its application to the rapid synthesis of a pyrido[1,2-*a*]indole skeleton common to a subclass of *Iboga* 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 chlormethylallylsilane **2a** under the influence of $TiCl_4$ resultng in smooth allylation. The usefulness of such an intermediate was not lost on us; a simple intramolecular S_N2 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 $Yb(OTf)_3$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, 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, vinylic and spiro-fused cyclopropanes. Reactivity is presumably dependent on stability of a putative ring-opened intermediate; cyclopropanes capable of supporting benzylic,

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



entry	cyclopropane (**3**)	allylation product (**4**)	cyclohexene (**5**)
1	**3a** R^1 = Phenyl R^2 = H	**4a:** 92%	**5a:** 95%
2	**3b** R^1 = 4-BrC_6H_4 R^2 = H	**4b:** 88%	**5b:** 95%
3	**3c** R^1 = 2-piperonyl R^2 = H	**4c:** 74%	**5c:** 97%
4	**3d** R^1 = 1-naphthyl R^2 = H	**4d:** 88%	**5d:** 91%
5	**3e** R^1 = 2-thienyl R^2 = H	**4e:** 62%	**5e:** 90%
6	**3f** R^1 = 4-indolyl R^2 = H	**4f:** 81%	**5f:** 91%
7	**3g** R^1 = Vinyl R^2 = H	**4g:** 83%	**5g:** 79%
8	**3h** R^1, R^2 = cyclohexyl	**4h** + **6** 72% (2:1 **4h**:**6**) (as inseparable mixture)	**5h:** 75%

[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

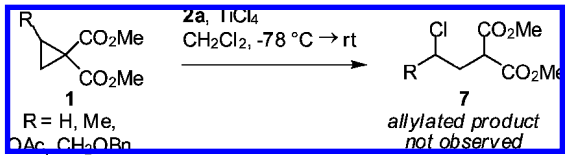
(8) (a) Boto, A.; Hernández, D.; Hernández, R.; Montoya, A.; Suárez, E. *Eur. J. Org. Chem.* **2007**, 325. (b) Sadakane, M.; Vahle, R.; Schierle, K.; Kolter, D.; Steckhan, E. *Synlett* **1997**, 95. (c) D'Aniello, F.; Mattii, D.; Taddei, M. *Synlett* **1993**, 119. (d) Guiles, J. W.; Meyers, A. I. *J. 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.

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 (R = OAc) cyclopropanes, this byproduct is obtained exclusively over prolonged reaction times with no indication of desired allylated product being formed by ^{1}H 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 us[12] 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 tronocarpine (**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 protocol[16] furnished cyclopropane

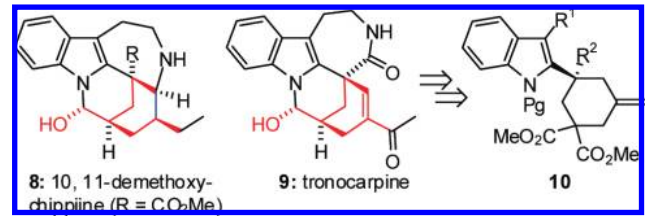
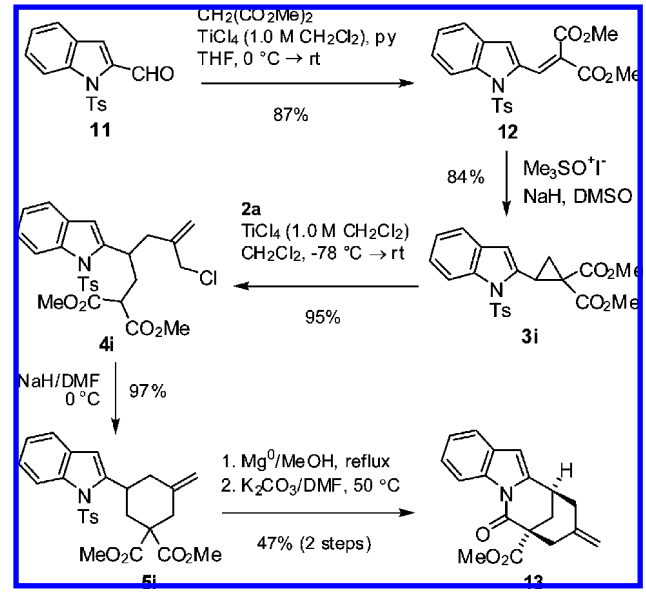


Figure 2. Representative *Iboga* alkaloids of *Tabernaemontana* sp. and possible synthetic precursor **10**.

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 contraints 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

(12) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561.
(13) Kam, T.-S.; Sim, K.-M. *Nat. Prod. Res.* **1999**, *13*, 143.
(14) Kam, T.-S.; Sim, K.-M.; Lim, T.-M. *Tetrahedron Lett.* **2000**, *15*, 2733.
(15) Riu, A.; Harrison-Marchand, A.; Maddaluno, J.; Gulea, M.; Albadri, H.; Masson, S. *Eur. J. Org. Chem.* **2007**, *29*, 4948.
(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.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada and Merck-Frosst for financial assistance. We thank Mr. Doug Hairsine of the University of Western Ontario mass spectrometry facility for performing MS analyses.

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.

OL900457Z