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Catalytic Crossed Michael Cycloisomerization of Thioenoates: Total Synthesis of (±)-Ricciocarpin A

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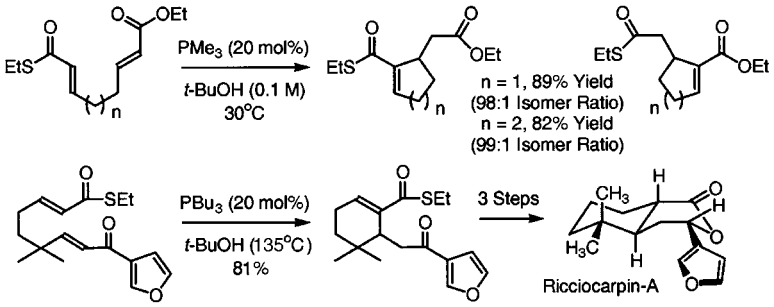
ABSTRACT



Thioenoates are found to participate in highly chemoselective catalytic crossed Michael cycloisomerization with appendant aryl ketone and enoate partners to afford cyclopentene and cyclohexene products. This methodology has enabled a concise total synthesis of the potent molluscicide (±)-ricciocarpin A.

Catalytic cycloisomerizations represent an important class of atom economical transformation.[1] Recently, the present author and Roush disclosed an intramolecular variant of the Rauhut−Currier reaction,[2] a phosphine-catalyzed "Michael cycloisomerization" of tethered α,β-unsaturated carbonyl partners.[3] A related study was subsequently reported by Murphy.[4] This transformation enables preparation of substituted cyclopentene and cyclohexene products under metal-free conditions. Remarkably, due to the exceptional sensitivity of this organocatalytic transformation with respect to the electrophilicity of the reacting partners, the highly chemoselective "crossed" cycloisomerization of nonsymmetric precursors was demonstrated.[3,4] Further extension of scope is potentially achieved by expanding the repertoire of reacting partners amenable to crossed cycloisomerization. In this account, we report the highly chemoselective crossed Michael cycloisomerization of thioenoates with appendant aryl ketone and enoate partners to afford cyclopentene and cyclohexene products. This methodology has enabled a concise total synthesis of the potent molluscicidal agent (±)-ricciocarpin A.

Impetus for these studies arose from difficulties encountered in the attempted Michael cycloisomerization of bis(enoates) **1a** and **2a**. While our initial studies establish enoates as viable electrophilic partners for Michael cycloisomerization,[3a] substrates **1a** and **2a** appear to be inert with respect to trialkylphosphine addition under a range of conditions. The low reactivity of **1a** and **2a** is attributed to the relatively low reactivity of the β-substituted enoate moiety, which prohibits conjugate addition of phosphine. As enoate electrophilicity should parallel the acidity of the parent

(1) For reviews, see: (a) Trost, B. M. *Science* **1991**, *256*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(2) For selected examples of the Rauhut−Currier reaction, see: (a) Rauhut, M. M.; Currier, H. (American Cyanamid Co.). U.S. Patent 3074999 19630122, 1963. (b) McClure, J. D. *J. Org. Chem.* **1970**, *35*, 3045. (c) Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett.* **1987**, *28*, 4591. (d) Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synth. Commun.* **1990**, *20*, 1915. (e) Jenner, G. *Tetrahedron Lett.* **2000**, *41*, 3091.

(3) (a) Wang, L.-C.; Luis, A.-L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404.

(4) Brown, P. M.; Kappel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, *43*, 8707.

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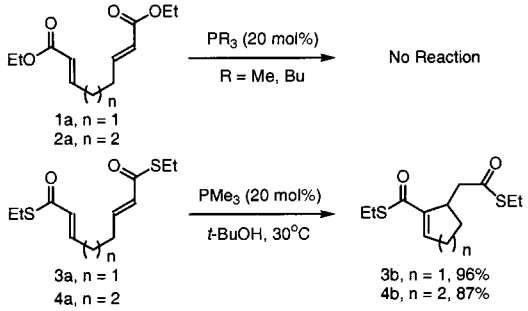
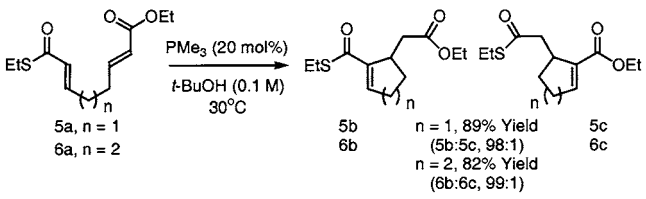
carbonyl compound, bis(thioenoates) were anticipated to be a more reactive substrate class.[5] Indeed, the enhanced performance of thioenoates in Morita−Baylis−Hillman-type cyclizations has been noted by Keck.[6] To test this hypothesis, bis(thioenoates) **3a** and **4a** were prepared through exhaustive olefination of succinaldehyde and glutaraldehyde, respectively, using previously reported stabilized Wittig reagents.[7] Gratifyingly, upon exposure of bis(thioenoates) **3a** and **4a** to catalytic trimethylphosphine at 30 °C in *tert*-butyl alcohol solvent (0.1 M), cyclization proceeds smoothly to provide good yields of the corresponding cyclopentene and cyclohexene products **3b** and **4b**, respectively (Scheme 1).[8]

Scheme 1. Catalytic Cycloisomerization of Bis(thioenoates) **3a** and **4a**



The marked difference in reactivity between enoate and thioenoate functional groups suggests that mixed monoenoate monothioenoates **5a** and **6a** may participate in catalytic crossed Michael cycloisomerization. Indeed, upon exposure of **5a** to the same conditions employed in the cyclization of bis(thioenoates) **3a** and **4a**, cycloisomerization product **5b** is obtained in 89% yield. The isomeric material **5c** could not be detected by ^{1}H NMR analysis. Analysis of the reaction product by gas chromatography reveals that **5b** is obtained in 98% isomeric purity. Under identical conditions, the homologous substrate **6a** provides cyclohexene **6b** in 82% yield. Again, the isomeric material **6c** could not be detected by ^{1}H NMR analysis. Analysis of the reaction product by gas chromatography reveals that **6b** is obtained in 99% isomeric purity (Scheme 2).

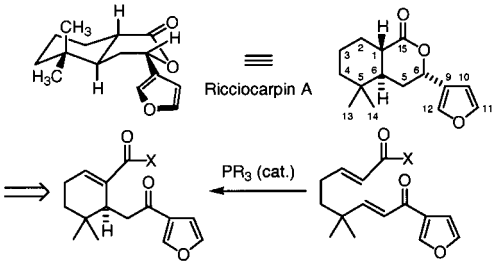
Scheme 2. Catalytic Cycloisomerization of Mixed Monoenoate Monothioenoates **5a** and **6a**



At this point, further methodological refinement was pursued in the context of a synthetic approach to the furanosesquiterpene lactone ricciocarpin A. Ricciocarpin A, isolated from the liverwort *Ricciocarpos natans*, exhibits potent molluscicidal activity against the water snail *Biomphalaria glabrata*, a vector of schistosomiasis.[9] Among humanparasitic diseases, schistosomiasis (sometimes called bilharziasis) ranks second behind malaria in terms of socioeconomic and public health importance in tropical and subtropical areas, infecting more than 200 million people in rural agricultural and periurban areas. Three safe, effective drugs are now available to those infected with schistosomiasis: praziquantel, oxamniquine, and metrifonate. However, the long-term objective is to diminish the population of the parasite vectors. Accordingly, the compound bayluscide (niclosamide) has been developed to kill infected water snails.[10] However, bayluscide is rather nonselective, having adverse affects on native fish, contaminating their flesh.[11] As such, ricciocarpin A has attracted considerable attention from synthetic chemists, which has resulted in several racemic syntheses[12] and a single enantioselective synthesis.[13]

Using the methodology herein, and inspired by related reductive Michael cyclization strategies,[12d] a concise total synthesis of ricciocarpin A was envisioned, in accordance with the retrosynthesis analysis depicted in Scheme 3. Here,

Scheme 3. Retrosynthetic Analysis of Ricciocarpin A



ricciocarpin A should derive via catalytic Michael cycloisomerization of an unsymmetrical bis(enone), which incorporates all carbons of the ricciocarpin skeleton. The indicated boat conformation of ricciocarpin A has been established through ^{1}H NMR and NOE difference spectroscopy.[14]

(5) Cronyn, M. W.; Chang, M. P.; Wall, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 3031.

(6) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687.

(7) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709.

(8) **Procedure.** Trimethylphosphine (20 mol %) was added to a 0.1 M solution of substrate in ^{t}BuOH under an atmosphere of argon, and the reaction was allowed to stir at 30 °C until complete. The reaction mixture was subjected to rotary evaporation, and the crude residue was purified by silica gel chromatography to give the cyclized product.

(9) (a) Wurzel, G.; Becker, H. *Phytochemistry* **1990**, *29*, 2565. (b) Wurzel, G.; Becker, H.; Eicher, T.; Tiefensee, K. *Planta Med.* **1990**, *56*, 444. (c) Zinsmeister, H. D.; Becker, H.; Eicher, T. *Angew. Chem.* **1991**, *103*, 134.

(10) Nabih, I.; Elwasimi, M. T. *J. Pharm. Sci.* **1968**, *57*, 1202.

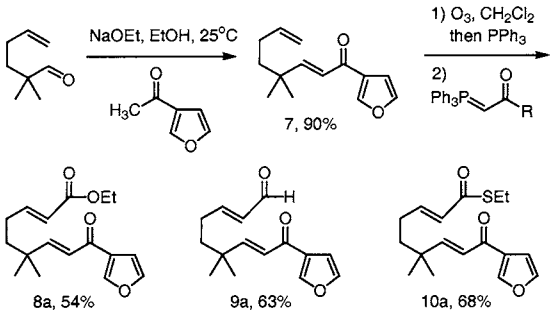
(11) Schreier, T. M.; Dawson, V. K.; Choi, Y.; Spanjers, N. J.; Boogaard, M. A. *J. Agric. Food Chem.* **2000**, *48*, 2212.

(12) For racemic syntheses of ricciocarpin A, see: (a) Eicher, T.; Massonne, K.; Herrmann, M. *Synthesis* **1991**, 1173. (b) Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2251. (c) Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *Chem. Commun.* **1993**, 755. (d) Takeda, K.; Ohkawa, N.; Hori, K.; Koizumi, T.; Yoshii, E. *Heterocycles* **1998**, *47*, 277.

(13) For an enantioselective syntheses of ricciocarpin A, see: Held, C.; Frohlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1058.

A modular approach to catalytic Michael cycloisomerization substrates **8a**−**10a** begins with the aldol condensation of 3-acetylfuran with 2,2-dimethyl-hex-5-enal to afford olefinic furyl enone **7**. Ozonolytic cleavage of **7**, followed by exposure of the resulting aldehyde to selected stabilized Wittig reagents, gave the cycloisomerization substrates **8a**−**10a**, which contain enoate, enal, and thioenoate moieties, respectively (Scheme 4).

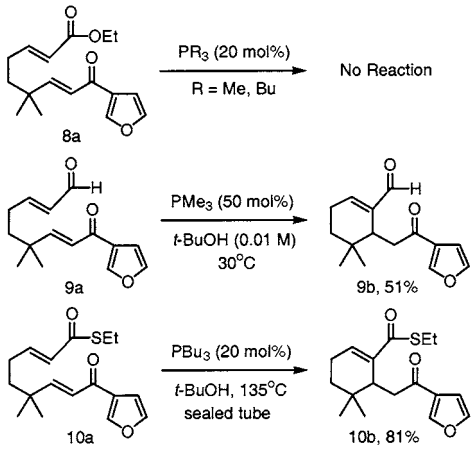
Scheme 4. Preparation of Cycloisomerization Substrates **8a**−**10a**



With compounds **8a**−**10a** in hand, their ability to participate in phosphine-catalyzed Michael cycloisomerization was examined. Consistent with the results pertaining to bis(enoates) **1a** and **2a**, exposure of monoenoate monofuryl enone **8a** to tributyl- or trimethylphosphine under a wide range of conditions gives only trace quantities of the corresponding cycloisomerization product **8b**. The related monoenal monofuryl enone **9a** embodies a more electrophilic pronucleophile. Upon exposure of **9a** to the conditions employed in the cyclization of thioenoates **3a**−**6a** (Schemes 1 and 2), cycloisomerization product **9b** is obtained in 38% yield, along with products of decomposition. Conducting the cycloisomerization under more dilute conditions and at higher catalyst loading affords a 51% yield of the corresponding cycloisomerization product **9b**. Finally, monothioenoate monofuryl enone **10a** was examined. Upon exposure of **10a** to the conditions employed in the cyclization of thioenoates **3a**−**6a** (Schemes 1 and 2), cycloisomerization product **10b** is obtained in 32% yield, along with recovered **10a**. The use of higher reaction temperatures overcomes the apparent lack of reactivity, providing cycloisomerization product **10b** in 81% yield (Scheme 5).

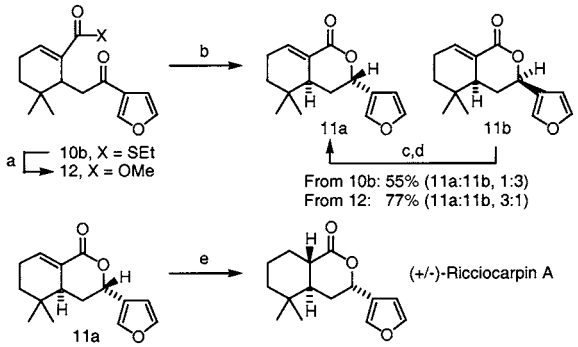
Ricciocarpin A may be derived from thioester **10b** via reductive lactonization of the keto-ester followed by conjugate reduction. Direct concomitant reductive lactonization−conjugate reduction of **10b** or **12** proved to be unsuccessful. Therefore, reductive lactonization of **10b** was attempted. Exposure of **10b** to the reduction conditions described by Luche[15] provides lactones **11a** and **11b** in 55% yield as a 1:3 mixture of diastereomers, respectively, along with products of over-reduction. The stereochemical assignment

Scheme 5. Phosphine-Catalyzed Michael Cycloisomerization of Furyl Enone Containing Substrates **8a**−**10a**



of diastereomers **11a** and **11b** was corroborated by NOE difference spectroscopy. In an effort to attenuate over-reduction, thioester **10b** was converted to the corresponding methyl ester **12**. Exposure of **12** to the aforementioned reduction conditions provides lactones **11a** and **11b** in 77% yield as a 3:1 mixture of diastereomers, respectively. The minor, undesired lactone isomer **11b** may be converted to **11a** via saponification−Mitsunobu inversion. Conjugate reduction of the unsaturated lactone **11a** using sodium borohydride in pyridine[16] provides (±)-ricciocarpin A, identical in all respects to previously reported material.[9,12,13] Notably, the conjugate reduction of **11a** to afford ricciocarpin A is completely stereoselective (Scheme 6).

Scheme 6. Reductive Lactonization of **10b** and **12**[a]



[a] Conditions: MeONa, MeOH, 25 °C, 88%. (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 25 °C. (c) LiOH, $THF \cdot H_2O$ (4:1), 25 °C. (d) DIAD, Ph_3P, CH_2Cl_2, 25 °C, 80% over two steps. (e) $NaBH_4$, pyridine, 25 °C, 78%.

In summary, thioenoates participate in highly chemoselective catalytic crossed cycloisomerization with appendant aryl ketone and enoate partners to afford cyclopentene and

(14) Wurzel, G.; Becker, H. *Phytochemistry* **1990**, *29*, 2565.
(15) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(16) Jackson, W. R.; Zuquiyah, A. *J. Chem. Soc., Chem. Commun.* **1965**, 5280.

cyclohexene products, enabling a concise synthetic approach to the furanosesquiterpene lactone ricciocarpin A. Future studies will be devoted to the discovery of other reacting partners amenable to crossed cycloisomerization and the development of enantioselective variants of the catalytic methodology reported herein.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and NOESY spectra for **11a** and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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