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An Efficient Synthesis of (±)-Grandisol Featuring 1,5-Enyne Metathesis

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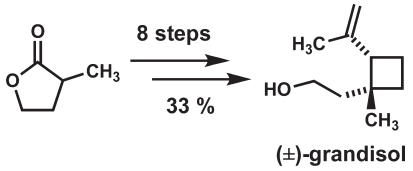
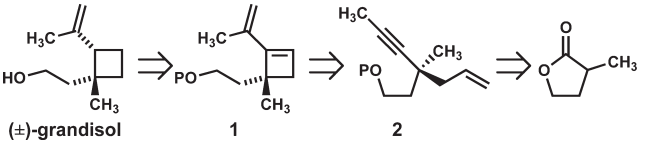


An eight-step synthesis of (±)-grandisol features a key sequence involving a high-yielding, microwave-assisted enyne metathesis to yield a 1-alkenylcyclobutene that is semihydrogenated to yield a silyl-protected grandisol. Metathesis catalyst screens revealed an intriguing trend whereby substrate conversion correlated strongly with the identity of the ligands on the catalyst. In addition, new reactivity of 1-alkenylcyclobutenes toward hydrogenation is described.

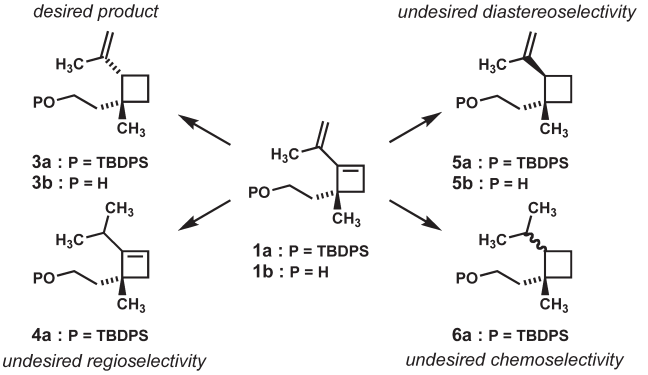
Grandisol is the primary constituent of the grandlure, a mixture of four pheromones that comprise the sex attractant of the cotton boll weevil. Cotton boll weevils cause significant damage to cotton crops, and grandlure-filled traps are one means used to protect against boll weevil infestation and its associated economic consequences. The extraction of grandlure components from large collections of dead weevils is tedious and unpleasant, making efficient synthetic routes an attractive alternative to harvesting. Furthermore, racemic grandisol has proven equally effective at attracting boll weevils as the natural enantiomer,[1] rendering moot the need for enantioselective syntheses for agricultural purposes.

Historically, the alkenylcyclobutane core of grandisol has presented a challenge to synthetic chemists and has served as a proving ground for new methodologies.[2] Herein we report the use of a 1,5-enyne metathesis reaction as the key step in a straightforward and efficient assembly of the carbon framework of grandisol. Our retrosynthetic analysis is described in Scheme 1. We envisioned the vinylcyclobutane core of grandisol arising from a semihydrogenation (monohydrogenation) of vinylcyclobutene **1**. Substituted vinylcyclobutene **1** can be prepared from enyne **2** in a metathesis cyclization. **2** may be prepared from commercially available α-methyl-γ-butyrolactone using standard synthetic manipulations.

SCHEME 1. Retrosynthesis of (±)-Grandisol



SCHEME 2. Challenges Associated with Selective Semihydrogenation of 1



The hydrogenation of **1** to **3** is a formidable synthesis challenge (Scheme 2); it must proceed with regioselectivity (preferential hydrogenation of the cyclic alkene over the acyclic alkene to instead form **4**), diastereoselectivity (preferential hydrogenation from the face of the cyclobutene bearing the methyl group over the ethyloxy group to instead form **5**), and chemoselectivity (preferential semihydrogenation of the diene over further hydrogenation of the intermediate monoene to instead form **6**). The reactivity of 1-alkenylcyclobutenes have not been extensively studied,[3] and no comprehensive strategy exists for the regioselective semihydrogenation of dienes in general and of conjugated dienes in particular.[4] However, for the conversion of **1** to **3**, we anticipated being able to obtain the desired regioselectivity by taking advantage of the enhanced reactivity of the cyclobutene due to its inherent ring strain.[5] Furthermore, we

(1) Hibbard, B. E.; Webster, F. X. *J. Chem. Ecol.* **1993**, *19*, 2129.

(2) Citations for 34 previously reported syntheses of grandisol may be found in ref 4 in the Supporting Information. Some of these syntheses are competitive with the present synthesis in terms of efficiency, and most describe a methodological advance. In particular, we direct interested readers to five manuscripts that are representative of the variety of excellent chemistries inspired by grandisol: refs. f, q, y, ff, and dd.

(3) For cycloadditions, see: (a) Park, J. D.; Frank, W. C. *J. Org. Chem.* **1964**, *29*, 1445. (b) Thummel, R. P. *J. Am. Chem. Soc.* **1976**, *98*, 628. (c) Thummel, R. P.; Nutakul, W. *J. Org. Chem.* **1977**, *42*, 300. (d) Thummel, R. P.; Cravey, W. E.; Nutakul, W. *J. Org. Chem.* **1978**, *43*, 2473. (e) Markgraf, J. H.; Greeno, E. W.; Miller, M. D.; Zaks, W. J. *Tetrahedron Lett.* **1983**, *24*, 241. (f) Doecke, C. W.; Garratt, P. J.; Shahriari-Zavareh, H.; Zahler, R. *J. Org. Chem.* **1984**, *49*, 1412. For an oxidation, see: (g) Takeda, A.; Tsuboi, S; Sakai, F.; Tanabe, M. *J. Org. Chem.* **1974**, *39*, 3098.

(4) Tungler, A.; Hegedüs, L.; Fodor, K.; Farkas, G.; Fürcht, Á.; Karancsi, Z. P. In *The Chemistry of Dienes and Polyenes*; Rapaport, Z., Ed.; John Wiley and Sons: New York, 2000; Vol. 2, p 992.

(5) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

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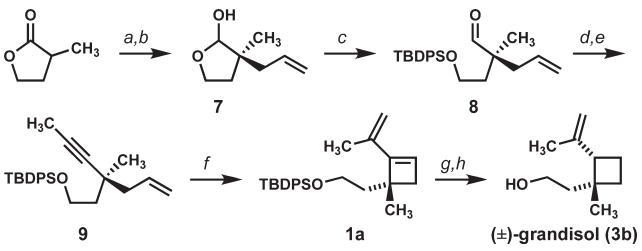
SCHEME 3. Synthesis of (±)-Grandisol[a]



[a]Reagents and conditions: (a) (i) LDA, (ii) allyl bromide, THF, −78 °C, 91%; (b) DIBAL-H, $PhCH_3$, −78 °C, 95%; (c) TBDPSCl, imidazole, DMF, 60 °C, 92%; (d) $CH_3COC(N_2)PO(OCH_3)_2$, K_2CO_3, CH_3OH, 87%; (e) (i) LDA, (ii) CH_3OTf, THF, −78 °C, 91%; (f) 10 (20 mol%), CH_2Cl_2, microwave, 75 °C, 83%; (g) Raney Ni, ^{i}PrOH, hexanes, 63%; (h) see ref 12.

expected that increasing the steric bulk of the alcohol through its conversion to a bulky silyl ether (for instance, P = TBDPS, **1a**) might promote diastereoselective hydrogenation from the opposite, less hindered face. Finally, though we hoped the inherent difference in reactivity of the strained cyclobutene would allow us to easily achieve the desired chemoselectivity, given the known sensitivity of hydrogenation reactions to substrate structure, catalyst, and solvent[6] and how little is known about the inherent reactivity of vinylcyclobutenes, we anticipated an empirical screen of reaction conditions might be necessary.

Our synthesis (Scheme 3) began with allylation of α-methyl-γ-butyrolactone followed by reduction of the lactone to yield lactol **7**. Silylation of the open-chain form of **7** gave aldehyde **8**. Alkynylation of the aldehyde with the Bestmann−Ohira reagent followed by methylation of the terminal alkyne generated enyne **9**, the substrate for our key methathesis cyclization.

When 1,5-enyne **9** was exposed to conditions previously reported by Campagne et al. to induce a metathesis cyclization for a variety of substrates[7] (catalyst **10**, microwave irradiation, CH_2Cl_2, 75 °C, 30 min), vinylcyclobutene **1a** was isolated in 83% yield. Notably, this yield is higher than any reported in the literature,[7] possibly due to the Thorpe−Ingold effect.[8] Encouraged by this result, we performed a comprehensive catalyst screen to determine which catalyst structural feature(s) facilitated the transformation. All but one catalyst bearing a mesityl-disubstituted N-heterocyclic carbene ligand (**10**→**13**) led to complete consumption of **9** within 30 min at 75 °C as determined by crude ^{1}H NMR (Figure 1). Of the remaining catalysts, those bearing a tricyclohexylphosphine ligand (**15**→**17**) showed moderate conversions, and those bearing an *o*-tolyl ligand showed poor conversions (**18**, **19**). NMR analyses of crude reaction mixtures revealed evidence of catalyst decomposition especially in reactions catalyzed by **15**→**17**, indicating the success

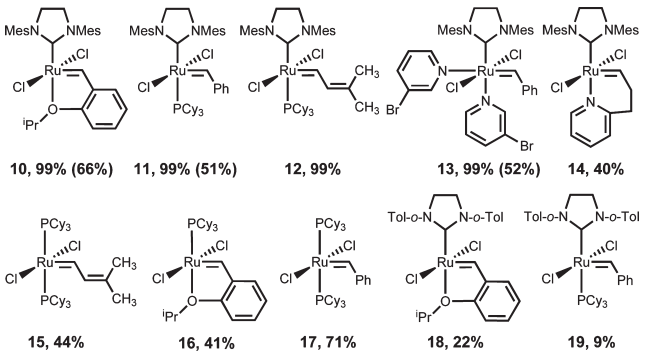


FIGURE 1. Result of catalyst screen. Percentages shown are conversion yields of the microwave reaction estimated from analysis of the crude NMR. Values in parentheses are isolated yields obtained using our sealed tube conditions (vide infra).

TABLE 1. Results of Representative Regioselective Semihydrogenations of 1a after 10 Minutes of Reaction Time

catalyst[c]	solvent	temp	**1a**[a]	**3a**	**4a**[b]	**6a**
Pd/C	THF	25 °C	15%	31%	10%	44%
Pd/C	THF	0 °C	14%	35%	11%	40%
Pd/C	$PhCH_3$	25 °C	42%	19%	10%	29%
Pd/C	EtOH	25 °C	0%	35%	12%	53%
Pd/C	hexane	25 °C	0%	43%	12%	45%
Pd/$CaCO_3$	EtOH	25 °C	0%	43%	5%	52%
Raney Ni[d]	^{i}PrOH	25 °C	0%	70%	8%	22%

[a]Percentages based on relative NMR integrations of distinctive peaks and scaled to 100%. [b]Product **5a** was formed in < 5% yield in each run. [c]5 mol %. [d]Performed in the absence of a hydrogen atmosphere.

of catalysts **10**→**13** is likely due to their enhanced stability at the elevated temperatures that are rapidly achieved with microwave irradiation. Such trends have been observed previously in microwave-assisted olefin metatheses.[9]

In an effort to expand the utility of this reaction to those without access to a microwave reactor, we developed a thermal, sealed tube protocol (sealed tube, CH_2Cl_2, 75 °C, 30 min) that gives lower yields than the microwave conditions described above yet significantly higher yields than the open flask yields reported in the literature.[7] Three of the four catalysts that led to complete consumption of **9** were evaluated under our sealed tube conditions (Figure 1). Though the sealed tube yields are lower than what can be achieved under microwave conditions, they are synthetically useful and complement the seminal results previously reported.[7]

The hydrogenation of **1a** proved challenging, with standard hydrogenation procedures generally leading within minutes to complete consumption of **1a** and formation of significant amounts of fully hydrogenated **6a** along with lesser amounts of desired **3a** (see Scheme 2) and other isomers (Table 1). Simple variations on solvent, temperature, and catalyst did not lead to increased production of **3a**. On the basis of previous observations that the adsorbed hydrogen on the surface of Raney Ni alone is sufficient to prevent full hydrogenation of alkynes,[10] we hoped that complete reduction to **6a** might be prevented through use of Raney Ni

(6) For a comprehensive treatment, see: (a) Kluwer, A. M.; Elsevier, C. J. In *The Handbook of Homogeneous Hydrogenation*; de Vreis, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley and Sons: New York, 2001. (c) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*; John Wiley and Sons: New York, 1978.

(7) Debleds, O.; Campagne, J. *J. Am. Chem. Soc.* **2008**, *130*, 1562.

(8) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080. (b) For an example in the context of a metathesis reaction, see: Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.

(9) For a review of microwave-assisted olefin metatheis, see: (a) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. Also see the following references therein: (b) Efskind, J.; Undheim, K. *Tetrahedron Lett.* **2003**, *44*, 2837. (c) Michaut, M; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2007**, 2867.

(10) (a) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028. (b) Soukup, M.; Widmer, E. *Tetrahedron Lett.* **1991**, *32*, 4117.

without a hydrogen atmosphere. We were pleased to discover that this was indeed the case; the desired isomer **3a** was isolated in 63% yield.[11] Conditions for cleaving the silyl protective group have been previously reported, and it occurs in quantitative yield.[12]

Notably, the undesired diastereomer **5a** was not observed in any significant quantity during the Raney Ni hydrogenation of **1a**, indicating the stereoselectivity of the transformation is indeed controlled by the substrate. To provide further support for this hypothesis, we deprotected **1a** (TBAF, THF, 81%) to form alcohol **1b** and attempted the Raney Ni hydrogenation on this substrate. ^{1}H NMR analyses of crude reaction samples throughout the reaction indicated no diastereoselectivity (essentially 1:1 production of **3b**/**5b**), which stands in stark contrast to the diastereoselective reaction observed with **1a**, which bears a large protective group.[13]

We have, therefore, described a synthetic sequence wherein (±)-grandisol may be prepared in eight steps and 33% overall yield from commercially available α-methyl-γ-butyrolactone. Key advances in this synthesis include development of a non-microwave-assisted method for a 1,5-enyne metathesis that proceeds in high yield and discovery of new insights into the reactivity of 1-alkenylcyclobutenes, a compound class whose reactivity has not yet been extensively studied.

(11) This compound has been previously reported (see ref 12). ^{1}H and ^{13}C NMR spectra, included in the Supporting Information, match the data reported in the literature. HRMS data were not previously reported for this compound and have been included in the Supporting Information.

(12) (a) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471. (b) Kim, D.; Kwak, Y. S.; Shin, K. J. *Tetrahedron Lett.* **1994**, *35*, 9211.

(13) The ^{1}H NMR analyses of these crude reaction mixtures were simplified by the fact that **5b** is fragranol,[14] a known natural product, whose chemical shifts are distinct from those of **3b** (grandisol).

(14) Bernard, A. M.; Frongia, A.; Secci, F.; Delogu, G.; Ollivier, J.; Pieras, P. P.; Salaün, J. *Tetrahedron* **2003**, *59*, 9433.

Experimental Section

Procedure for Thermal, Sealed Tube Preparation of 1a. *Note: sealed tube experiments should always be conducted behind a safety shield.*

To a solution of **9** (467 mg, 1.19 mmol) in anhydrous CH_2Cl_2 (31 mL) was added **10** (150 mg, 20 mol %). The flask was then briefly purged with argon and sealed. The flask was then submerged in a preheated 75 °C oil bath and allowed to stir for 35 min. The flask was removed, cooled in an ice bath, and concentrated to give a green residue. Biotage column chromatography (2% Et_2O/pentane) afforded **1a** as a colorless oil (309 mg, 66%).

Acknowledgment. Financial support from ACS-PRF (47106-GB1), Research Corporation (CC7044/7165), and NIH-NCRR (P20 RR-016461) to B.G. is gratefully acknowledged. We thank the Milliken Foundation for providing critical instrumentation, and Biotage, LLC for use of a microwave reactor. T.G. acknowledges Furman University for a research fellowship.

Supporting Information Available: Detailed experimental procedures for the preparation of all new compounds reported in Schemes 2 and 3 along with corresponding characterization data and the complete citation for ref 2. This material is available free of charge via the Internet at http://pubs.acs.org.