Stereoselective Butenolide Reduction

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Dynamic Kinetic Resolution of α,β-Unsaturated Lactones through Asymmetric Copper-Catalyzed Conjugate Reduction: Application to the Total Synthesis of Eupomatilone-3**

*Matthew P. Rainka, Jacqueline E. Milne, and Stephen L. Buchwald**

Eupomatilones 1–7 are a family of lignans[1] isolated from the Australian shrub *Eupomatia bennettii,* found in the tropical and subtropical forests of New South Wales and Queensland.[2] All seven members of this family contain a highly oxygenated biaryl motif, as well as a *cis* orientation of the substituents at C4 and C5 of the butyrolactone ring. Of all the members of the eupomatilone family, there have only been three for which a total synthesis has been reported: eupomatilone-6, eupomatilone-4, and 3-*epi*-eupomatilone-6.[3] Despite this work, the total synthesis of enantiomerically enriched members of the eupomatilone family has remained an unsolved problem. Herein, we report the first asymmetric

[*] M. P. Rainka, J. E. Milne, Prof. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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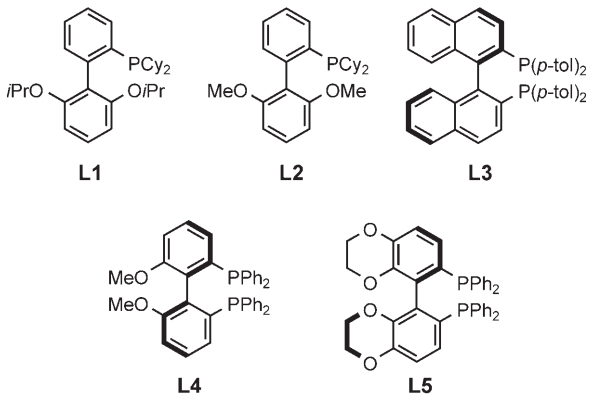
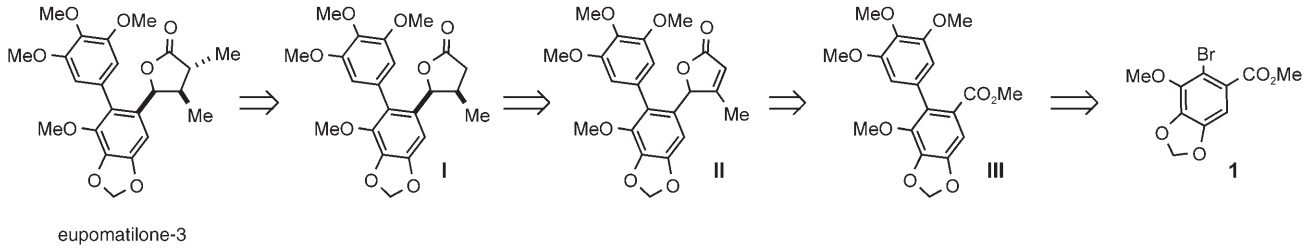
total synthesis of one member of the family, eupomatilone-3. The success of the synthesis was based on a highly efficient Suzuki–Miyaura cross-coupling,[4] along with a dynamic kinetic resolution[5] of an unsaturated lactone.

Our interest in the synthesis of eupomatilone-3 emanated from the compound's interesting structural features, in particular the biaryl motif, along with the *cis* orientation of the substituents at C4 and C5 of the lactone portion of the molecule. Our retrosynthetic analysis of eupomatilone-3 is shown in Scheme 1. On the basis of our recent work in the area of palladium-catalyzed cross-coupling reactions,[6] it was believed we could assemble the highly oxygenated biaryl portion of the molecule **III** by utilizing either a Negishi or Suzuki–Miyaura coupling. Furthermore, we envisioned generating the desired lactone stereochemistry in **I** through either a diastereoselective or an enantioselective copper-catalyzed conjugate reduction reaction.[7]

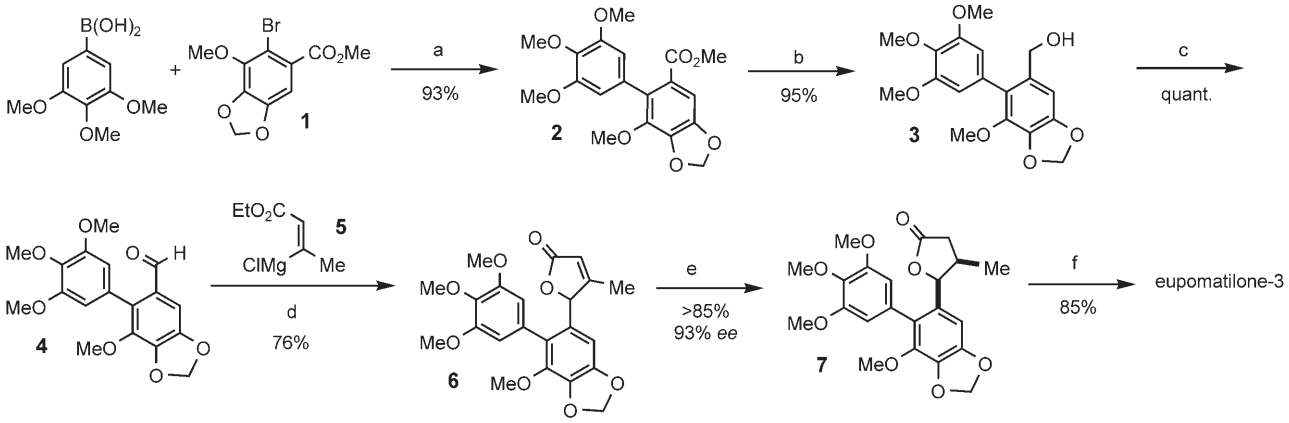
The synthesis was begun by investigating the cross-coupling of known aryl bromide **1**[8] with organometallic reagents derived from bromo-3,4,5-trimethoxybenzene. By employing reaction conditions found to be optimal with palladium catalysts derived from the bulky phosphanylbiaryl ligands RuPhos **L1** (Negishi)[6b] or SPhos **L2** (Suzuki–Miyaura)[6a,c] allowed for efficient production of biaryl **2** (Scheme 2). The Negishi coupling produced **2** in 93% yield at a catalyst loading of 1 mol% palladium. With the corresponding Suzuki–Miyaura reaction, it was found that **2** could be obtained in 93% yield even when the catalyst loading was lowered to 0.005 mol% palladium (0.00025 mol% $[Pd_2(dba)_3]$; dba = dibenzylideneacetone).



With a means to rapidly construct the biaryl portion of eupomatilone-3, investigation began into the preparation of the butenolide **6**. When examining this motif, we turned to Knochel's method for the synthesis of butenolides by the reaction of stabilized vinyl Grignard reagents with aldehydes.[9] To apply this method to this synthesis, the methyl ester **2** first needed to be transformed to the corresponding aryl aldehyde **4**. Conversion of **2** into the benzyl alcohol **3** was accomplished by borane reduction in THF. Intermediate **3** was oxidized with MnO_2 to give the desired benzaldehyde derivative **4** in essentially quantitative yield. Treatment of this



Scheme 1. Retrosynthetic analysis of eupomatilone-3.



Scheme 2. Synthesis of eupomatilone-3 (yields are the average of two runs determined to be >95% pure by ^{1}H NMR or GC). a) $[Pd_2(dba)_3]$ (0.0025 mol%), SPhos **L2** (0.02 mol%), K_3PO_4 (2 equiv), THF, 80°C. b) BH_3·THF, THF, 60°C. c) MnO_2, CH_2Cl_2, RT. d) THF, −40°C. e) $CuCl_2$·2 H_2O (5 mol%), MeO-BIPHEP **L4** (5 mol%), NaO*t*Bu (1.2 equiv), PMHS (6 equiv), *t*BuOH, THF, CH_2Cl_2, RT. f) NaHMDS, THF, 0°C, then MeI. PMHS: polymethylhydrosiloxane; NaHMDS: sodium hexamethyldisilazide.

aldehyde with the vinyl Grignard reagent **5** (formed in situ from the corresponding vinyl iodide[10]) according to Knochel's procedure provided the desired unsaturated lactone in 76% yield.

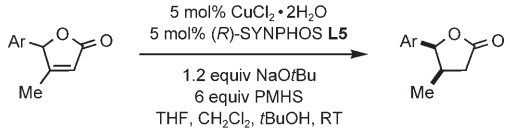
The next hurdle in the synthesis was the conversion of butenolide **6** into *cis*-4,5-disubstituted lactone **7**. The installation of this stereochemistry was explored by using an asymmetric conjugate reduction reaction.[11,12] We have previously demonstrated the asymmetric reduction of unsaturated lactones using a chiral copper–hydride catalyst.[12b] Furthermore, we have succeeded in carrying out both kinetic as well as dynamic kinetic resolutions of 3,5-disubstituted cyclopentenones by employing similar catalysts.[12d] Despite unsatisfactory results when reducing 3,4-disubstituted cyclopentenones,[12d] we decided to attempt the kinetic resolution of **6** under our standard conjugate reduction conditions[12] at −30 °C in a 1:1 mixture of THF/CH_2Cl_2 (dichloromethane was necessary due to the poor solubility of the lactone in THF). After 50% conversion of **6**, the desired *cis* compound **7** was isolated in 46% yield and with 87% *ee*. Interestingly, the process was completely diastereoselective: none of the *trans* isomer was ever detected.

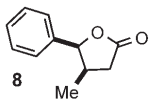
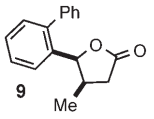
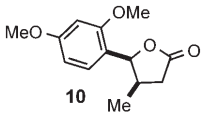
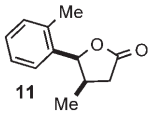
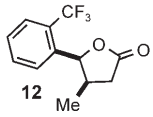
With this promising result, we sought to extend the method to the dynamic kinetic resolution of unsaturated lactones. We felt that performing the reaction in the presence of excess base (NaO*t*Bu) should allow for racemization of the starting material such that complete conversion may be effected. Unfortunately, no racemization occurred when 1.2 equivalents of NaO*t*Bu was used at −30 °C, even after prolonged reaction times. When the same experiment, however, was conducted at room temperature, complete conversion of the starting material into the desired product was observed. As in the case of the simple kinetic resolution, the product was obtained as a single diastereomer and with 83% *ee*. This represents the first copper-catalyzed dynamic kinetic resolution of an unsaturated lactone.

In an attempt to improve the enantioselectivity of the reaction, other chiral bisphosphine ligands were used. It was found that replacing *p*-tol-BINAP **L3** with MeO-BIPHEP **L4** while still performing the reaction at room temperature provided the desired compound, again as a single diastereomer, but now with 93% *ee* (when the kinetic resolution was carried out at −30 °C with **L4**, the product was obtained with 95% *ee*). With the *cis* lactone prepared, all that remained to complete the synthesis was to install the final methyl group in the α position on the lactone ring. This was accomplished by enolization of lactone **7** with NaHMDS followed by alkylation with iodomethane to give synthetic eupomatilone-3 in 85% yield; its spectra were in agreement with those published for material obtained from the natural source.[2,13]

On the basis of the success of the dynamic kinetic resolution reaction described above, we briefly examined the scope of this process by using other γ-aryl-containing unsaturated lactones. Initial results employing **L4** as the supporting ligand provided poor enantioselectivity for substrates other than the natural product, however the diastereoselectivity remained high. A brief survey of the efficiency of ligands for this process was undertaken and it was observed that the commercially available SYNPHOS ligand **L5** provided the highest enantioselectivities (except in the case of the natural product, in which **L4** gave the best result).[14] The scope of the reaction was examined and the results are shown in Table 1. Aside from **8**, all products were formed with enantioselectivities ranging from 77 to 87%. Thus, no clear dependence on steric or electronic factors could be ascertained.

Table 1: Dynamic kinetic resolution of unsaturated lactones.



Product	*ee* [%]	Yield [%][a]
 **8**	67	95
 **9**	81	92
 **10**	87	85
 **11**	77	91
 **12**	78	94

[a] Yields are the average of two runs determined to be greater than 95% pure by ^{1}H NMR spectroscopy or GC.

Unfortunately, use of the same reaction conditions for the dynamic kinetic resolution of lactones that contain simple alkyl substituents in the γ position failed to give more than 50% conversion of the starting material. This is presumably due to poor racemization of the starting lactone. Additionally, the reaction provided both the *cis* and *trans* isomers of the product, and the enantiomeric enrichment of the *cis* product was found to be low (< 25% *ee*).

In conclusion, the total synthesis of eupomatilone-3 was achieved in six steps and in 48% overall yield. The key to the success of the synthesis was the development of a dynamic kinetic resolution that allowed the α,β-unsaturated butenolide **6** to be reduced in high yield and with both high enantiomeric and diastereomeric excess. This is the first example of a copper-catalyzed dynamic kinetic resolution of an unsaturated lactone. The method was then applied to several γ-aryl containing α,β-unsaturated butenolides. While a number of catalysts based on chiral bisphosphines were found to successfully promote this transformation, optimal

enantioselectivity was obtained when employing the commercially available SYNPHOS ligand **L5**.

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[1] For a review on lignans, see: R. S. Ward, *Nat. Prod. Rep.* **1997**, *14*, 43.
[2] A. R. Carroll, W. C. Taylor, *Aust. J. Chem.* **1991**, *44*, 1705.
[3] For recent synthetic efforts, see: a) S.-P. Hong, M. C. McIntosh, *Org. Lett.* **2002**, *4*, 19; b) J. M. Hutchison, S. P. Hong, M. C. McIntosh, *J. Org. Chem.* **2004**, *69*, 4185; c) M. K. Gurjar, J. Cherian, C. V. Ramana, *Org. Lett.* **2004**, *6*, 317; d) R. S. Coleman, S. R. Gurrala, *Org. Lett.* **2004**, *6*, 4025.
[4] For reviews, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) N. Miyaura in *Metal-Catalyzed Cross-Coupling Reactions, Vol. 1*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, chap. 2, pp. 41 – 123; c) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263; d) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; e) M. Miura, *Angew. Chem.* **2004**, *116*, 2251; *Angew. Chem. Int. Ed.* **2004**, *43*, 2201; f) F. Bellina, A. Carpita, R. Rossi, *Synthesis* **2004**, 2419.
[5] For reviews, see: a) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291; b) R. S. Ward, *Tetrahedron: Asymmetry* **1995**, *6*, 1475; c) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc.* **1989**, *111*, 9134.
[6] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) J. E. Milne, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 13028; c) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, *116*, 1907; *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.
[7] O. Riant, N. Mostefaï, J. Courmarcel, *Synthesis* **2004**, 2943.
[8] a) A. Alam, Y. Takaguchi, H. Ito, T. Yoshida, S. Tsuboi, *Tetrahedron* **2005**, *61*, 1909; b) G. M. Keseru, M. Nogradi, M. Kajtar-Peredy, *Liebigs Ann. Chem.* **1994**, 361; c) J. Chang, X. Guo, S. Cheng, R. Guo, R. Chen, K. Zhao, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2131; d) J. Chang, R. Chen, R. Guo, C. Dong, K. Zhao, *Helv. Chim. Acta* **2003**, *86*, 2239.
[9] I. Sapountzis, W. Dohle, P. Knochel, *Chem. Commun.* **2001**, 2068.
[10] E. Piers, T. Wong, P. D. Coish, C. Rogers, *Can. J. Chem.* **1994**, *72*, 1816.
[11] For related work involving chiral copper–hydride catalysts, see: a) B. H. Lipshutz, H. Shimizu, *Angew. Chem.* **2004**, *116*, 2278; *Angew. Chem. Int. Ed.* **2004**, *43*, 2228; b) B. H. Lipshutz, J. M. Servesko, *Angew. Chem.* **2003**, *115*, 4937; *Angew. Chem. Int. Ed.* **2003**, *42*, 4789; c) B. H. Lipshutz, C. C. Caires, P. Kuipers, W. Chrisman, *Org. Lett.* **2003**, *5*, 3085; d) C. Czekelius, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 4941; *Angew. Chem. Int. Ed.* **2003**, *42*, 4793; e) B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352.
[12] a) M. P. Rainka, Y. Aye, S. L. Buchwald, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5821; b) G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253; c) V. Jurkauskas, J. P. Sadighi, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 2417; d) V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 2892; e) Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797; f) D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473; g) J. Yun, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1129.
[13] While the absolute configuration of the natural material is unknown, the optical rotation measurements on the synthetic material were in agreement with those on material from the natural source.
[14] a) C.-C. Pai, Y.-M. Li, Z.-Y. Zhou, A. S. C. Chan, *Tetrahedron Lett.* **2002**, *43*, 2789; b) S. D. de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Tetrahedron Lett.* **2003**, *44*, 823; c) SYNPHOS was purchased from Strem Chemicals, Inc.; d) While SEGPhos (another common ligand employed in conjugate reduction chemistry with copper) is not commercially available, in the near future we hope to test this ligand in the dynamic kinetic resolution process.

