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Application of Enantioselective Radical Reactions: Synthesis of (+)-Ricciocarpins A and B

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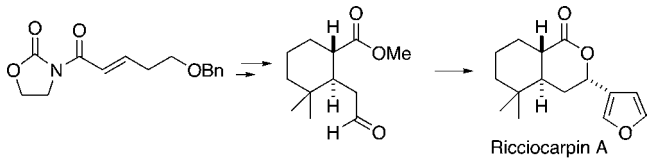
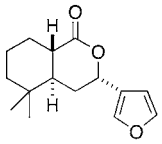
ABSTRACT



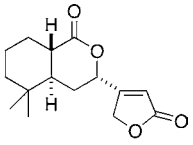
Enantioselective synthesis of (+)-ricciocarpins A and B has been achieved in 41 and 45% overall yields, respectively, starting from a β-substituted oxazolidinone. The key steps in the strategy are an enantioselective conjugate radical addition and the addition of a furyl organometallic to a key aldehyde intermediate.

In the past decade, we have witnessed a rapid growth in stereoselective free radical chemistry.[1] In this context, methods for enantioselective bond construction using free radical intermediates have begun to emerge.[2] The use of enantioselective radical reactions at the strategy level in the synthesis of natural products is yet to be demonstrated in a routine fashion. Our group and others have reported several novel methods for carbon−carbon bond construction using enantioselective conjugate radical additions.[3] In this work, we highlight the application of enantioselective radical chemistry in the synthesis of two novel sesquiterpene lactones.

Ricciocarpin A, a furanosesquiterpene lactone, has been isolated from an axenic culture of the European liverwort, *Ricciocarpos natas* (Ricciaceae). The natural product exhibits high molluscicidal activity against the water snail *Biomphalaria glabtata*, a vector of schistosomiasis.[4] Ricciocarpin B, which differs from ricciocarpin A in the oxidation state of the furan ring, has also been isolated from liverwort. Several racemic syntheses of ricciocarpin A have been reported.[5] Metz and co-workers have reported the only enantioselective synthesis of ricciocarpin A.[6] The conversion of ricciocarpin A to ricciocarpin B has also been reported by Metz.[6] In this work, we report a short and efficient synthesis of both ricciocarpins A and B in enantiomerically pure form.



1 Ricciocarpin A



2 Ricciocarpin B

Our strategy for the synthesis of ricciocarpins A and B is shown in Scheme 1. Our plan was to prepare a key aldehyde intermediate **3** and optimize the addition of furan organo-

(1) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

(2) For recent reviews see: (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251. (c) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8303.

(3) (a) Sibi, M. P.; Ji, J. G.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (b) Sibi, M. P.; Ji, J. G. *J. Org. Chem.* **1997**, *62*, 3800. (c) Sibi, M. P.; Shay, J. J.; Ji, J. G. *Tetrahedron Lett.* **1997**, *38*, 5955. (d) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (e) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929. (f) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *15*, 2879. (g) Sibi, M. P.; Zimmerman, J.; Rheault, T. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 4521. (h) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (i) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299.

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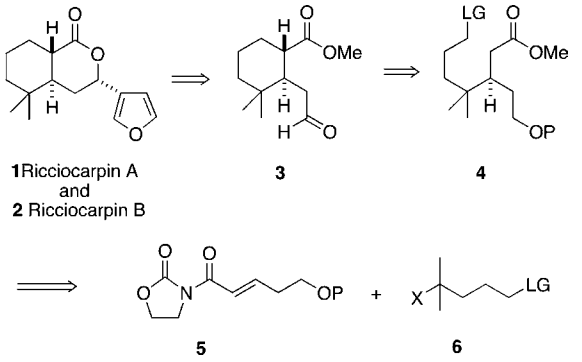
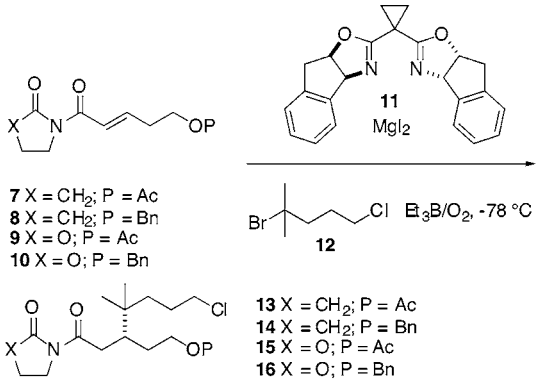
Scheme 1



metallics leading to the two targets.[7] The aldehyde **3** would be accessed through a stereoselective cyclization of **4**. Enantioselective conjugate addition of a functionalized radical **6** to enoate **5**, followed by routine functional group manipulations, would furnish the intermediate **4**.

Our work began with the identification of an optimal substrate for enantioselective conjugate addition with a functionalized radical (Scheme 2). On the basis of our prior work, we chose to investigate pyrrolidinone and oxazolidinone substrates **7**−**10**.[8] The functionalized radical precursor **12** was prepared by a two-step sequence starting with the commercially available 5-chloro-2-pentanone.[9] We have previously shown that a chiral Lewis acid derived from magnesium salts and bisoxazoline **11** is very effective in enantioselective conjugate radical additions. Reactions of **7**−**10** with the tertiary radical derived from **12** using 100 mol % of the chiral Lewis acid gave products **13**−**16** (entries 1−4). The efficiency of the reaction was dependent on the template and the oxygen protecting group. Substrate **10** with an *O*-benzyl protecting group gave the highest yield and enantioselectivity (entry 4).[10] Reactions with lower catalyst loading (50 mol %, entry 5; 30 mol %, entry 6) gave the

Scheme 2[a]



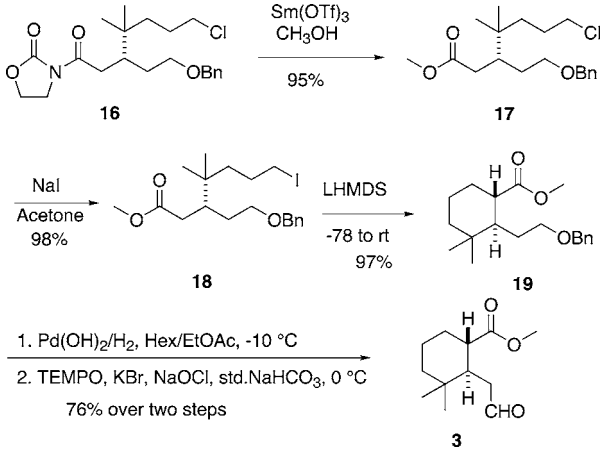
entry	sm	X	P	prod.[a]	yield, (%)[b]	ee, %[c]
1[d]	**7**	CH_2	$COCH_3$	**13**	31	84
2[d]	**8**	CH_2	$CH_2C_6H_5$	**14**	<10	-
3[d]	**9**	O	$COCH_3$	**15**	70	95
4[d]	**10**	O	$CH_2C_6H_5$	**16**	84	97
5[e]	**10**	O	$CH_2C_6H_5$	**16**	50	97
6[f]	**10**	O	$CH_2C_6H_5$	**16**	16	93

[a] For reaction conditions, see Supporting Information. [b]Isolated yield after column purification. [c]Determined by chiral HPLC. [d]Performed with 100 mol % of the chiral Lewis acid. [e]Performed with 50 mol % of the chiral Lewis acid. [f]Performed with 30 mol % of the chiral Lewis acid.

desired product **16** in lower yields but with similar levels of selectivity.

With the desired conjugate addition product **16** in hand, we set out to prepare the key aldehyde intermediate **3** (Scheme 3). The oxazolidinone **16** was converted to the methyl ester **17** in excellent yield using a protocol developed by Otera.[11] Halogen interchange under Finkelstein conditions produced the iodoester **18** in high yield. The crucial six-membered ring construction[12] was carried out using LHMDS as the base yielding **19** as a single trans isomer.[13] Debenzylation under carefully controlled conditions,[14] followed

Scheme 3



(4) (a) Wurzel, G.; Becker, H.; Eicher, T.; Tiefensee, K. *Planta Med.* **1990**, *56*, 444. (b) Wurzel, G.; Becker, H. *Phytochemistry* **1990**, *29*, 2565. (c) Zinsmeister, H. D.; Becker, H.; Eicher, T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 130. (d) Thiel, R.; Adam, K. P.; Zapp, J.; Becker, H. *Pharm. Pharmacol. Lett.* **1997**, *7*, 103.

(5) Racemic synthesis: (a) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (b) Takeda, K.; Ohkawa, N.; Hori, K.; Koizumi, T.; Yoshii, E. *Heterocycles* **1998**, *47*, 277. (c) Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem., Soc., Perkin Trans. 1* **1993**, 2251. (d) Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1993**, 755. (e) Eicher, T.; Massonne, K.; Herrmann, M. *Synthesis* **1991**, 1173.

(6) (a) Held, C.; Frohlich, R.; Metz, P. *Adv. Synth. Catal.* **2002**, *344*, 720. (b) Held, C.; Frohlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1058.

(7) A similar disconnection has been applied in the racemic synthesis of **1** starting with **3** (or a slight variant) and 3-furyllithium (see refs 5b−e). The yield for this transformation has been <30%.

(8) These compounds were prepared in a straightforward fashion using well-established literature procedures. See Supporting Information for details.

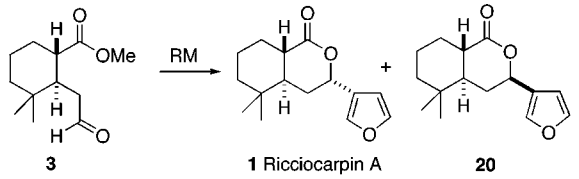
(9) See Supporting Information for details.

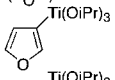
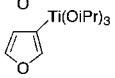
(10) Stereochemical outcome in *tert*-butyl radical additions to oxazolidinone crotonates or cinnamates using ligand **11** and MgI_2 has been previously shown to provide products with *R* configuration. We initially assigned the stereochemistry for **16** on the basis of the above precedents, which was later confirmed by the synthesis of the natural product.

by immediate oxidation, provided the key aldehyde intermediate **3** in good overall yield over two steps.

The conversion of aldehyde **3** to racemic ricciocarpin A has been reported in the literature. In this transformation, 3-lithiofuran was used as the nucleophile. The average yield for the addition was <30%, and the diastereoselectivity in general was modest.[15] However, Takeda and co-workers have reported that **1** can be obtained as the sole isomer in 29% yield. The low yield and selectivity in the addition of 3-lithiofuran to **3** led us to examine this transformation in some detail (Scheme 4). Addition of 3-lithiofuran to **3** in

Scheme 4[a]



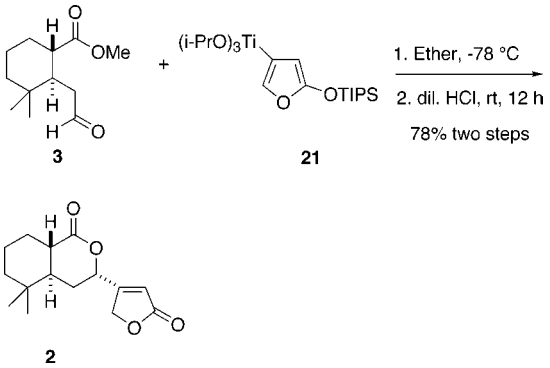
entry	RM	temp °C	solv.	time, h	yield, (%)[b]	ratio[c] **1**:**20**
1		-78	THF	6	33	1:3
2		-78	Ether	5	26	1:7.8
3		-78	Ether	3	21	1:6
4[d]		0	Ether	10	8	1:3
5		-78	THF	4	28	1:1
6		-78	Ether	4	85	5.7:1

[a] For reaction conditions, see Supporting Information. [b] Isolated yield after column purification. [c] Determined by NMR. [d] Pseudoephedrine was used as a ligand.

either THF or ether as a solvent gave a mixture of diastereomeric lactones **1** and **20** in modest yields. We did not obtain **1** as the major isomer as had been reported in the literature (entries 1 and 2). The use of the Grignard reagent (entry 3)[16] or the zinc reagent (entry 4)[17] did not lead to improvements in either the yield or the diastereoselectivity favoring the target. Boukouvalas and co-workers in their synthesis of dysidiolide have shown that furyl titanium reagents[18] add efficiently to aliphatic aldehydes. On the basis of this precedent, we evaluated the addition of the 3-titanyloxyfuran reagent to **3** (entries 5 and 6). These reactions were very rewarding, and we obtained the highest chemical yield for the lactone products with the desired natural ricciocarpin **1** as the major product. The two diastereomers could be separated using preparative HPLC. The spectral and analytical characteristics of synthetic (+)-ricciocarpin A were identical to those reported in the literature. The overall yield for **1** starting from **10** is 41.5%.

Metz and co-workers have reported the conversion of ricciocarpin A to B.[6a] The ready availability of the aldehyde **3** and the known chemistry of 2-alkoxy-4-lithio (or titanyloxy) reagent led us to explore the synthesis of ricciocarpin B (Scheme 5). The required 4-bromo-2-silyloxyfuran was

Scheme 5



synthesized following a literature procedure.[19] The titanium organometallic **21** was prepared according to the protocol previously described by Boukouvalas.[18a] The reagent **21** was prepared at room temperature and added to a solution of the aldehyde **3** at −78 °C. The crude reaction mixture was treated with dilute hydrochloric acid and stirred at room temperature for 12 h. This resulted in silyl group deprotection and cyclization to furnish ricciocarpin B **2** as a single isomer in 78% yield. The spectral and analytical characteristics of **2** were in complete agreement with those reported in the literature.[4a,6a]

In conclusion, we have developed an efficient synthesis of ricciocarpin A and B that highlights the use of enantioselective conjugate radical addition methodology. The syn-

(11) (a) Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637. (b) Also see: Sibi, M. P.; Hasegawa, H.; Ghorpade, S. R. *Org. Lett.* **2002**, *4*, 3343.

(12) Attempts to form the six-membered ring with an acyl-oxazolidinone (instead of the methyl ester) gave complex product mixtures.

(13) Relative stereochemistry was established by coupling constant analysis. The proton at C-1 resonates at δ 2.31 ppm (dt, J_t = 12.0 Hz, J_d = 3.6 Hz, 1H). The 12 Hz coupling constant clearly establishes the relative stereochemistry at the ring as trans.

(14) Temperature of the reaction is important to avoid the premature formation of the lactone.

(15) For the addition of 3-furyllithium to aliphatic aldehydes, see: (a) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. (b) Demeke. D.; Forsyth, C. J. *Org. Lett.* **2000**, *2*, 3177. (c) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111. (d) Liu, H.-J.; Zhu, J.-L.; Chen, I.-C.; Jankowska, R.; Han, Y.; Shia, K.-S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1851.

(16) For the addition of 3-furylmagnesium bromide to imines, see: (a) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303. (b) Oppolzer, W.; Froelich, O.; Wiaux-Zamar, C.; Bernardinelli, G. *Tetrahedron Lett.* **1997**, *37*, 2825.

(17) Preparation of 3-furylzinc reagent: Negishi, E.-i.; Takahashi, T.; King, A. O. *Org. Synth.* **1988**, *66*, 67. Difuryl zinc reagents: Xue, S.; Han, K.-Z.; He, L.; Guo, Q.-X. *Synlett* **2003**, 870.

(18) (a) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. For a recent review, see: (b) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595.

(19) Kanoh, N.; Ishihara, J.; Yamamoto, Y.; Murai, A. *Synthesis* **2000**, 1878.

thesis of other sesquiterpenes with biological activity, which feature enantioselective radical chemistry, is underway in our laboratory.

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Supporting Information Available: Characterization data for compounds **1**−**3** and **7**−**20** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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