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TETRAHEDRON: *ASYMMETRY*

First synthesis of (*R*)-(−)-5-hydroxy-3-methyl-3-pyrrolin-2-one (jatropham) by lipase-catalyzed kinetic resolution

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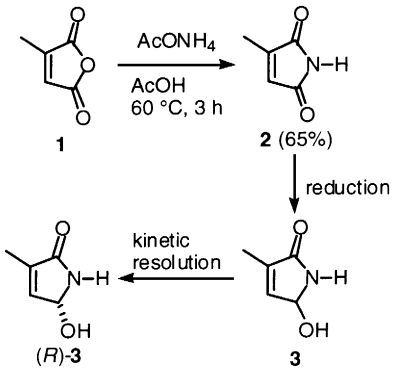
Abstract

Jatropham, (*R*)-(−)-5-hydroxy-3-methyl-3-pyrrolin-2-one, is synthesized in three steps from citraconic anhydride. Highly regioselective reduction of citraconimide gives racemic jatropham in high yield. Kinetic resolution of racemic jatropham using lipase is also described. © 1999 Elsevier Science Ltd. All rights reserved.

Jatropham, (*R*)-(−)-5-hydroxy-3-methyl-3-pyrrolin-2-one (*R*)-**3**, is an antitumor alkaloid isolated from *Jatropha macrohiza* (Euphorbiaceae) in 1973 by Cole et al.[1,2] The synthesis of (±)-jatropham has included the conversion of lactone to lactam,[3] the autoxidation of 2-furylcabamate,[4] and selenoxide *syn* elimination[5] etc.;[6] however, several steps are needed for the preparation and the yields are relatively low in these reports. Moreover, the synthesis of homochiral natural jatropham **3** has not yet been reported. We now report herein the first synthesis of natural jatropham (*R*)-**3** from citraconic anhydride **1** in three steps (Scheme 1), of which the regioselective reduction of citraconimide **2** and the kinetic resolution of racemic jatropham **3** are the key steps for the successful synthesis.



Scheme 1.

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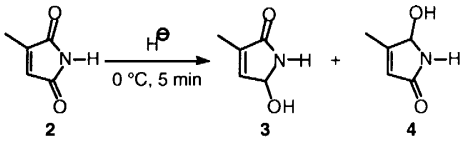
Citraconimide **2** was prepared from citraconic anhydride **1**, which is commercially available and inexpensive, by the procedure reported in the literature.[7] Previously, the regioselective reduction of citraconimide **2** using $NaBH_4$ was examined by Nagasaka et al.,[5] where only 5-hydroxy-4-methyl-3-pyrrolin-2-one **4** was obtained. Indeed, our experiment also showed high regioselectivity caused by attack of the hydride anion at the C2 carbon to give the regioisomer **4** in 96% yield (Table 1, entry 1). On the other hand, in the presence of $CeCl_3$ a considerable amount of jatropham **3** was obtained (entry 2).[8] Furthermore, reduction using DIBAL afforded only jatropham **3** in 95% yield (entry 3); probably, the bulky DIBAL approached the C5 carbon to avoid steric influence.

Table 1
Regioselective reduction of citraconimide **2**

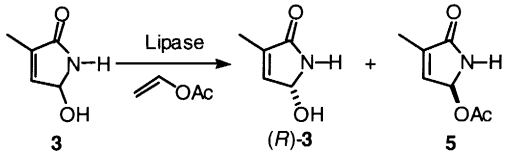


Entry	Reducing Agent	Solvent	Yield (%)	**3** : **4**[a]
1	$NaBH_4$	MeOH	96	<1 : >99
2	$NaBH_4/CeCl_3$	MeOH	52	82 : 18
3	DIBAL	THF	95	>99 : <1

[a] Determined by HPLC analysis (YMC-Pack SIL, hexane : 2-propanol = 50 : 50, 0.3 mL/min)

Next, the lipase-catalyzed kinetic resolution of (±)-jatropham **3** was examined (Table 2).[9] (±)-Jatropham **3** was treated with vinyl acetate in the presence of lipases. In the case of lipases M and A, the transesterification did not occur (entries 1 and 2). On the other hand, the reaction using lipase PS smoothly proceeded to give (*R*)-jatropham **3** and the (*S*)-acetate **5** (entries 3–5). The reactivity as well as enantioselectivity was improved by using lipase PL, and (*R*)-jatropham **3** was obtained in 35% yield with 98% e.e. along with the (*S*)-acetate **5** in 53% yield with 50% e.e. (entry 6).[10]

Table 2
Kinetic resolution of (±)-jatropham **3**



Entry	Lipase	Solvent	Yield of (*R*)-**3** (%)	e.e.[a] (%)	E value
1	M	1,4-dioxane	no reaction	—	—
2	A	1,4-dioxane	no reaction	—	—
3	PS	1,4-dioxane	36	52	4
4	PS	*i*-Pr_2O	35	37	3
5	PS	—	19	96	61
6	PL	—	35	98	168

[a] Determined by HPLC analysis (Chiralpak AS, hexane : 2-propanol = 70:30, 1.0 mL/min).

In summary, we have shown the regioselective reduction of citraconimide **2** and the kinetic resolution of (±)-jatropham **3**. These reactions have provided a simple and inexpensive preparation of (*R*)-jatropham **3**.

Acknowledgements

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8. Isolation of reduction product **3** from the crude product was relatively difficult in the case of $NaBH_4/CeCl_3$ reduction.
9. A solution of (±)-jatropham **3** and lipase (0.5 gram equivalent) in vinyl acetate (10 equivalent) was stirred at 25°C, then lipase was removed by filtration, and concentrated to give a crude oil, which was purified by column chromatography (silica gel) to give (*R*)-jatropham (*R*)-**3** and the acetate **5**.
10. Previously, the absolute configuration of (−)-jatropham **3** was deduced from CD spectrum analysis.[2a] We confirmed the absolute configuration by comparison of the known value of the specific rotation of 1-benzyl-3-methylpyrrolidine-2,5-dione (*R*)-**7** (lit. $[\alpha]_D^{22}$=+14.4 (*c* 1.39, $CHCl_3$, 80% ee)) after transformations of (*R*)-**3** (37% ee) obtained in Table 2, entry 4. A negative value ($[\alpha]_D^{18}$=−6.1 (*c* 1.24, $CHCl_3$)) of (*S*)-**7** was observed; therefore, (−)-jatropham **3** had (*R*) configuration, see: Puertas, S.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1995**, *51* (5), 1495–1502.