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KINETIC RESOLUTION OF 2-FURYLCARBINOLS USING THE SHARPLESS OXIDATION AND ITS APPLICATION TO THE SYNTHESIS OF (5R,6S)-6-ACETOXY-5-HEXADECANOLIDE

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Abstract —— Kinetic resolution of 2-furylcarbinols employing 10 mol % of $Ti(O^iPr)_4$ in the presence of molecular sieves 3A under the Sharpless oxidation condition generally affords corresponding optically active 2-furylcarbinols in a range of 80-98% ee. Application of the optically active 1f to the synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide (8), the major component of the oviposition attractant pheromone of the mosquito *Culex pipens fatigans*, has also been achieved.

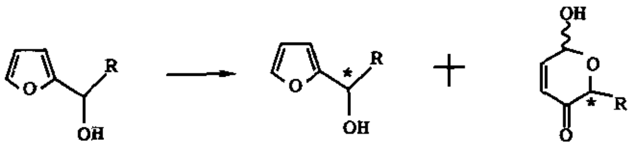
Recently we have developed the stereoselective syntheses of physiologically active steroids, where the oxidation of 2-furylcarbinol has been employed as a key reaction.[1] As our continuing work on the utilization of this strategy in the synthesis of natural products, we have investigated kinetic resolution[2] of 2-furylcarbinols employing the Sharpless reagent[3] to prepare optically active 1.[4] Here we report successful results for the catalytic asymmetric kinetic resolution of racemic 1 affording optically active 1 and its application to the synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide as an oviposition attractant pheromone of the mosquito *Celux pipens fatigans*.[5]

Our results for catalytic asymmetric kinetic resolution[3b] of racemic 1 a-f which were carried out in the presence of 3A molecular sieves using TBHP (0.7 eq), $Ti(O^iPr)_4$ (10% mol), and tartrate (15% mol) are summarized in Table I. The reactions proceed rapidly to produce the optically active 2-furylcarbinols of high enatiomeric purity except for 1a and 1d, whose reaction conditions might not be optimized. It is noteworthy that reaction of 2-furylpropenylcarbinol 1d afforded the kinetically resolved 1d and its corresponding lactol 2d. This result suggests that the rate for oxidation of 2-furylcarbinol is faster than that for epoxidation of allylic alcohol. The absolute configurations of 1 were deduced by the comparison with the specific rotations of the corresponding products,[4j,4k] and confirmed unambiguously by transformation of the optically active 1f into (5R,6S)-6-acetoxy-5-hexadecanolide (8).

As outlined in Scheme 1, treatment of 1f (>98% optical purity) with N-bromosuccinimide in aqueous tetrahydrofuran afforded the corresponding lactol 2f, whose catalytic hydrogenation followed by dithioacetalization gave the α-hydroxy ketone 3, $[\alpha]_D^{25}$ + 32.3° (c 1.56, $CHCl_3$), in 77% overall yield. Reduction of 3 with zinc borohydride[6] in ether furnished an inseparable mixture of the diols, which was acetonized to give a chromatographically separable (1:4.6) mixture of acetonides 4, $[\alpha]_D^{25}$ - 22.0° (c 0.64, $CHCl_3$), and 5, $[\alpha]_D^{25}$ + 11.1° (c 1.3, $CHCl_3$) in 87% yield. Hydrolysis[7] of the dithioacetal 5 with red mercuric oxide and boron trifluoride in aqueous tetrahydrofuran afforded the corresponding aldehyde, whose reaction with 2-lithio-2-trimethylsilyl-1,3-dithiane gave the ketene thioacetal 6, $[\alpha]_D^{25}$ + 7.1° (c 0.5, $CHCl_3$), in 61% yield. Finally, treatment[8] of 6 with mercuric chloride in methanol and water followed by lactonization of the crude product furnished (5R,6S)-6-hydroxy-5-hexadecanolide 7, mp 68-69 ℃ (from n-hexane), $[\alpha]_D^{22}$ - 12.5° (c 0.2, $CHCl_3$) [lit.[5b] mp 67-68 ℃ (n-hexane), $[\alpha]_D^{20}$ - 12.5° (c 0.54, $CHCl_3$)], in 50% overall yield. Since acetylation of 7 was already accomplished by several groups,[5] this constitutes a synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide (8).

Thus, we have developed a simple and efficient method for preparation of the optically active 2-furylcarbinols employing catalytic asymmetric kinetic resolution of the racemic 2-furylcarbinols. The absolute configurations of the resolved 2-furylcarbinols could be predictable by regarding the tartrate employed.[3] As an application of the optically active 2-furylcarbinols to natural products synthesis, we demonstrated an efficient synthesis of (5R,6S)-6-acetoxy-5-hexadecanolide (8) starting from (S)-(2-furyl)-undecanol 1d in 9 steps. The optically active 2-furylcarbinols thus resolved serve as highly versatile intermediates for the synthesis of a variety of natural products.

Table I. Kinetic Resolution of 2-Furylcarbinols[a]

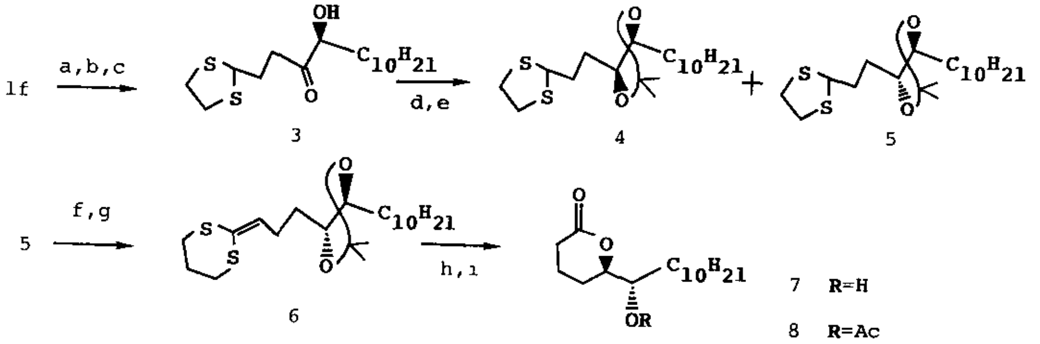


1a-f optically active 1a-f 2a-f

racemic 1a-f R		temp. °C	time (h)	optically active 1a-f[b] yield %[c]	%ee[d]	$[\alpha]_D^{25}$ (C,$CHCl_3$)	abs. config.	2 yield %[c]
a	methyl	-20	5	36	80	+17.4°(1.78)	R	38
b	ethyl	-20	3.5	32	95	+12.6°(2.09)	R	42
c	butyl	-35	6	43	94	+ 9.2°(1.07)	R	46
d	propenyl	-30	7	32	82[f]	-40.4°(1.95)	R	52
e	cyclohexyl	-25	7	44	>98[e]	+20.0°(1.19)	R	52
f	decyl	-25	4	44	>98	- 9.6°(2.49)	S[g]	51

[a] All reactions were carried out with 10% Ti(O^{i}Pr)$_4$, 15% L-(+)-DIPT, and 0.7 equiv. of TBHP / isooctane in the presence of 3A molecular sieves, except as noted. [b] All recovered 2-furylcarbinols had the depicted (R) stereochemistry, except 1f. [c] Isolated yields. [d] Determined by 400 MHz ^1H nmr analysis of the corresponding MTPA ester. [e] >98% ee indicates that the other enantiomer was not detectable by nmr. [f] Determined by 400 MHz ^1H nmr analysis of the MTPA ester of 2-furylpropylcarbinol after hydrogenation of the optically active 1d because of the instability of the product on reaction with MTPA chloride. [g] D-(-)-DIPT was employed.

Scheme 1



(a) NBS, THF-H_2O; (b) H_2, 10% Pd-C, AcOEt; (c) $HS(CH_2)_2SH$, $BF_3\cdot OEt_2$, CH_2Cl_2; (d) $Zn(BH_4)_2$, Et_2O, -25 °C; (e) acetone, p-TsOH; (f) HgO, $BF_3\cdot OEt_2$, THF-H_2O; (g) Li, Me_3Si (dithiane), THF; (h) $HgCl_2$, MeOH-H_2O, 100 °C; (i) p-TsOH, benzene, 80 °C.

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