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Oxidative Resolution of 2-Cyclopentenols By the Asymmetric Hydrogen Transfer Protocol

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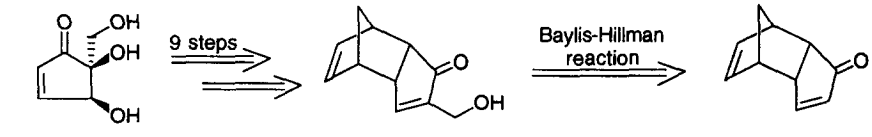
Abstract: A Ru^{II}-chiral amine complex has accomplished oxidative resolution of the 2-cyclopentene-1-ols having a bicyclo[2.2.1]heptene background to afford the cyclopentenones and the cyclopentenols both in good to excellent optical and chemical yields by an asymmetric hydrogen transfer reaction. The hydrogen transfer occurred selectively at the allylic methine hydrogen even though allylic methylene hydrogens are present at the same relative position.

Keywords: catalysis; enantioselection; oxidation; ruthenium and compounds; transfer reactions

We have recently completed a diastereocontrolled synthesis[1] of (–)-pentenomycin I **1**, an antibiotic metabolite produced by *Streptomyces eurythermus*, starting from (+)-ketodicyclopentadiene[2] (KDP) **3**. In the synthesis, we employed the Baylis-Hillman reaction[3] to convert enantiopure KDP (+)-**3** into the key α-hydroxymethylenone (+)-**2a** in ~65% yield (**Scheme 1**). Since we intend to use this chiral hydroxymethylenone **2a** as a versatile chiral building block, we explored its alternative chiral preparation without losing chiral KDP **3**. In this paper, we wish to report a new chiral route to **2a** and its derivatives from racemic KDP (±)-**3** by employing Noyori's Ru^{II}-chiral amine-mediated asymmetric hydrogen transfer protocol.[4–6]



(–)-pentenomycin I **1** (+)-**2a** (+)-KDP **3**

Scheme 1

0040-4039/99/$ - see front matter
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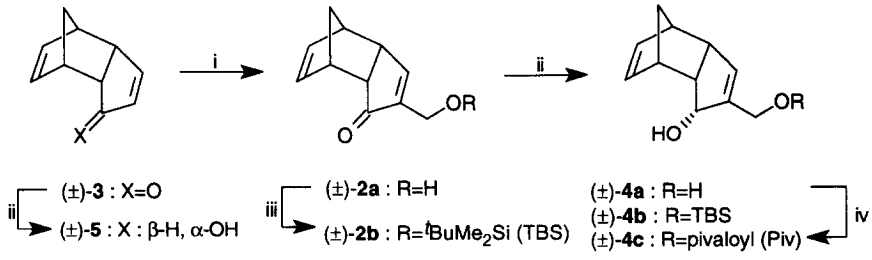
Ru^{II}-complexes of chiral mono-*N*-tosyl-1,2-diphenylethylenediamines[4,7] catalyze the hydrogen transfer reaction of racemic allylic and benzylic secondary alcohols to acetone enantioselectively by converting one enantiomer into achiral ketones, leaving the other enantiomer intact. Therefore, only one-half of the starting racemic secondary alcohols at best can be recovered in single enantiomeric forms. However, we could transform both enantiomers into chiral products if we choose the substrates having a particular stereochemical background. The allylic alcohol **4a** is a representative case as it can keep molecular chirality owing to its bicyclo[2.2.1]heptane background even though it loses its allylic chirality to give the enone **2a** by the hydrogen transfer reaction.[8] To realize this basic idea, we examined oxidative resolution of the racemic tricyclic allyl alcohol **4a** and its two protected forms **4b** and **4c** employing the conditions established by Noyori and co-workers.[4,7] Three racemic substrates **4a~c** were prepared from racemic KDP (±)-**3** by the sequence involving the Baylis-Hillman reaction[3c] and convex-face selective 1,2-reduction (**Scheme 2**).

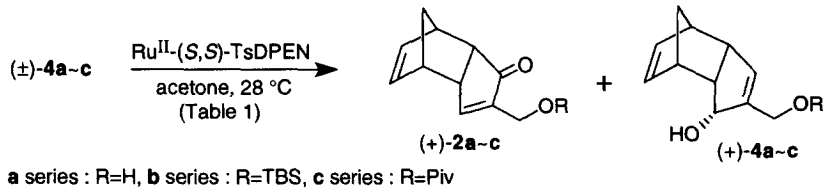


Scheme 2

Reagents and conditions: i) 30% formalin, DMAP, THF, 3d, (67%). ii) DIBAL, toluene, –78 °C, (97% for **4a** and **4b**, 91% for **5**). iii) TBS-Cl, imidazole, DMF, (96%). iv) Piv-Cl, pyridine, (95%).

We first examined the hydrogen transfer reaction of the diol **4a**, having two hydroxy functionalities at the same relative position, in acetone at 28 °C in the presence of the Ru^{II}-(1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine[Ru^{II}-(*S*,*S*)-TsDPEN] catalyst prepared from [{$RuCl_2(\eta^6$-*p*-cymene)$\}_2$].[7] Besides oxidative resolution, we were in particular interested in the fate of the primary and secondary allylic hydroxy functionalities under the conditions since no such precedent has been reported. The reaction was found to occur chemoselectively at the secondary center to give the chiral enone (+)-**2a** leaving the chiral diol (+)-**4a** without affection of the primary hydroxy functionality (**Table 1**: Entries 1~3). Although the reaction was still far from adequate for practical use owing to the low substrate-catalyst ratio (< 50) (**Table 1**: Entries 2 and 3) and low substrate solubility in acetone (~ 0.2 M), it afforded two chiral products as expected.

On the other hand, two analogues, (±)-**4b** and (±)-**4c**, having a protected primary *O*-functionality are more soluble in acetone, and the reaction was carried out in 2.0 M concentration in a 200:1 substrate-catalyst ratio for the TBS ether (±)-**4b** and in a 50:1 ratio for the pivalate (±)-**4c** to carry out satisfactory resolution to give rise to two chiral products in high enantiomeric excess and excellent chemical yields (**Table 1**: Entries 6 and 9), though the substrate-catalyst ratios were still less than satisfactory (**Scheme 3**).



a series : R=H, **b** series : R=TBS, **c** series : R=Piv

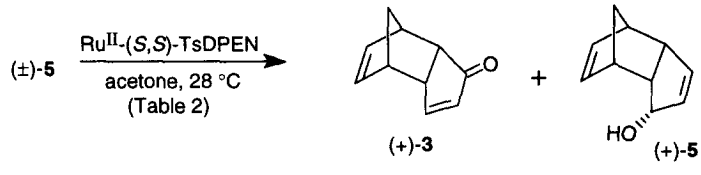
Scheme 3

Table 1: Oxidative Resolution of Tricyclic Cyclopentenols (±)-4a~c.[a]

Entry	Substrate **4**	Substrate/Catalyst (mol/mol)	Time (h)	Product (%[b] : % ee) Enone **2**	Alcohol[c] **4**
1	**a**	100	12	57 : 54[c]	41 : 84
2	"	50	12	46 : 92[c]	48 : 90
3	"	33	12	51 : 87[c]	43 : >99
4	**b**	400	12	14 : 89[d]	79 : 5
5	"	200	12	53 : 93[d]	43 : 78
6	"	200	4	48 : 95[d]	48 : 92
7	"	100	12	52 : 56[d]	30 : >99
8	**c**	100	24	34 : 98[c]	66 : 56
9	"	50	12	49 : 94[c]	49 : >99
10	"	25	12	54 : 77[c]	45 : >99

a) The reaction was carried out in 0.2 M solution for **4a** and in 2.0 M solution for **4b**,**c** at 28 °C in acetone. b) Yield after SiO_2 column chromatography. c) E.e. was determined by hplc after transformation into **2c** (CHIRALCEL OJ, ^{i}PrOH-hexane 1:200). d) E.e. was determined by hplc (CHIRALCEL OD, ^{i}PrOH-hexane 1:1000). e) E.e. was determined after transformation into the enones **2b** and **2c**.

In relation to the oxidative resolution of the racemic α-substituted cyclopentenols **4a~c**, we also examined the reaction of the non-α-substituted cyclopentenol **5** under the same conditions (**Scheme 4**). The reaction proceeded at much faster rate comparing with the α-substituted substrates **4a~c** in a higher substrate-catalyst ratio to give the chiral enone (+)-**3** and the chiral allyl alcohol (+)-**5** in good yields. But the optical purities of the products, in particular the enone (+)-**3**, were lower than those of the α-substituted substrates (**Table 2**: Entries 1~3). The observed lower enantioselectivity may be explained by the lower enantiomeric discrimination in the non-α-substituted substrate which was supported by an experiment using chiral substrates (–)- and (+)-**5** (**Table 2**: Entries 4~7). Thus, while the catalyst-matching (–)-**5** was readily transformed into the enone (+)-**3** in good yield as expected (**Table 2**: Entries 4 and 5), the mismatching (+)-**5** also afforded a considerable amount of the enantiomeric enone (–)-**3** (**Table 2**: Entries 6 and 7). These results indicated that an α-substituent is an essential factor to bring about high enantiomeric discrimination for the cyclopentenol substrates having a bicyclo[2.2.1]heptene background in the presence of Ru^{II}-(*S*,*S*)-TsDPEN catalyst.[8]



Scheme 4

Table 2: Oxidative Resolution of Tricyclic Cyclopentenols (±)-5.[a]

Entry	Substrate **5**	Substrate/Catalyst (mol/mol)	Time (min)	Product (%[b] : % ee) Enone (+)-**3**	Alcohol[c] (+)-**5**
1	(±)-**5**	300	50	57 : 54[d]	41 : 84
2	"	200	50	61 : 51	37 : 91
3	"	200	180	57 : 44	31 : 96
4	(−)-**5**	300	45	89 : n.d.[e]	0
5	"	100	150	95 : n.d.	0
6	(+)-**5**	300	45	35[f] : n.d.	62 : n.d.
7	"	100	150	33[f] : n.d.	53 : n.d.

a) The reaction was carried out in 2.0 M solution at 28 °C in acetone. b) Yield after SiO_2 column chromatography. c) E.e. was determined after conversion into the enone **3**. d) E.e. was determined by hplc (CHIRALCEL OB, ^{i}PrOH-hexane 5:95). e) n.d. stands for not determined. f) The enone (−)-**3** was obtained.

In summary, we have accomplished resolution of racemic 2-cyclopentene-1-ols having bicyclo[2.2.1]heptene background, without the loss of one of the enantiomers, by a Ru^{II}-chiral amine complex-mediated enantiospecific hydrogen transfer reaction to give versatile chiral cyclopentanoid chiral building blocks. We also have found that an α-substituent is an essential factor to bring about high enantiomeric discrimination.

Acknowledgement

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