ORGANIC LETTERS

2004
Vol. 6, No. 19
3365−3367

Highly Efficient Chemical Kinetic Resolution of Bishomoallylic Alcohols: Synthesis of (*R*)-Sulcatol

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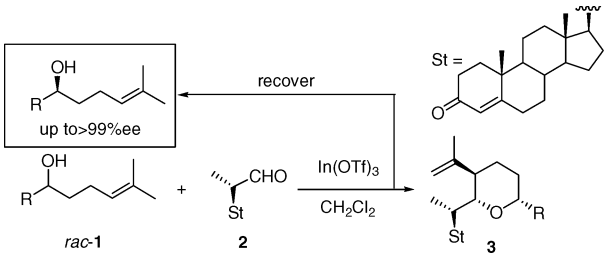
Received July 20, 2004

ABSTRACT



A highly efficient chemical kinetic resolution of bishomoallylic alcohols was developed when the alcohols underwent In(OTf)$_3$-catalyzed 3,5-oxonium-ene-type cyclization with steroidal aldehyde 2. Consistently high enantiomeric excess (up to >99%) was obtained.

Optically active allylic, homoallylic, and bishomoallylic alcohols are valuable intermediates in organic synthesis. The versatile transformation of their alkenyl functionality provides access to a variety of enantiomerically enriched compounds.[1] Currently, enantioenriched allylic and homoallylic alcohols can be easily prepared by asymmetric reduction or carbonyl addition.[2] As to bishomoallylic alcohols, enantioselective synthetic methods are still rarely reported. This is probably because of the lack of difference between two substituents of ketone in an asymmetric reduction and the much lower accessibility of suitable nucleophiles to carbonyl addition. Therefore, the kinetic resolution of readily available racemic alcohols[3] is an attractive alternative route to optically active bishomoallylic alcohols. Although enzymatic resolution of alcohols is well established, most existing chemical methods for kinetic resolution of alcohols can only be applied to benzylic or allylic alcohols.[4] Herein we present a highly efficient chemical kinetic resolution of bishomoallylic alcohols based on a remarkable remote 1,4-stereocontrol and its application to a simple synthesis of (*R*)-sulcatol.

Recently, our group reported that bishomoallylic alcohol and aldehydes can undergo facile (3,5)-oxonium ene-type cyclizations in the presence of a catalytic amount of

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(3) For some leading references, see: (a) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397−400. (b) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074−4077. (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420.

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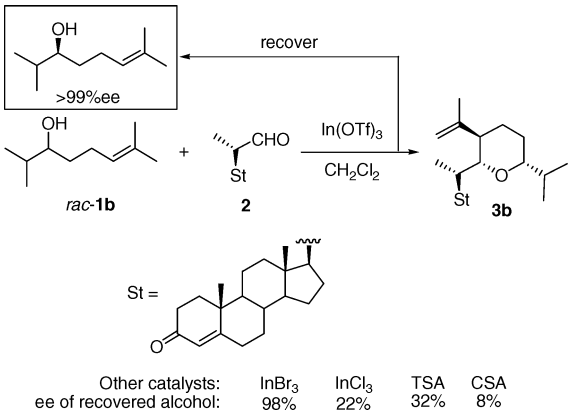
10.1021/ol048608q CCC: $27.50
Published on Web 08/24/2004

$In(OTf)_3$.[5] In conjunction with our ongoing project, we investigated the stereoinduction of chiral aldehydes in this reaction. In an initial experiment, a solution of the bishomoallylic alcohol **1b**[6] (0.3 mmol) and the commercially available steroidal aldehyde **2**[7] (0.3 mmol) in CH_2Cl_2 (1 mL) was stirred with a catalytic amount of $In(OTf)_3$ (10 mol %) at room temperature (Scheme 1). After 3−4 h, TLC analysis

Scheme 1. Kinetic Resolution of Bishomoallylic Alcohol **1b**



indicated that approximately half of the substrates have been consumed. No significant progress of the reaction was observed even with an elongation of the reaction time to 16 h. Furthermore, only one cyclization product was observed by TLC and crude ^1H NMR, which indicated a kinetic resolution of racemate alcohol. After chromatography purification, the recovered alcohol was found to have an enantiomeric purity of >99% ee.[8]

Encouraged by this preliminary result, we investigated the reaction conditions for the kinetic resolution of bishomoallylic alcohol **1b**. It was found that the enantiomeric excess of the alcohol **1b** was increased from 44, 80, 98 to >99% ee with increases in reaction times from 0.5, 1, 2, 3 to 4 h, respectively. This series of data indicated that the kinetic resolution is very rapid and reached maximum conversion in 4 h at room temperature. In turn, we also investigated the catalytic ability of different acids. Among them, $In(OTf)_3$ was found to have the best catalytic activity (Scheme 1).

With the optimized reaction conditions, we examined the applicability of this new kinetic resolution method for various substrates. The results are summarized in Table 1. This method worked very well with different R groups (from linear and bulky aliphatic substituents) and gave consistently high enantiomeric excesses ranging from 92 to >99% ee.

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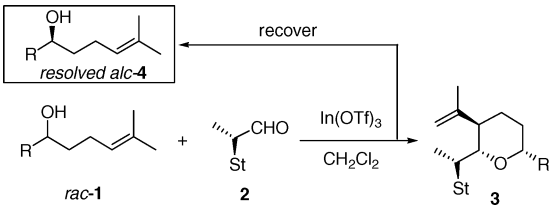
(6) Loh, T. P.; Song, H. Y.; Zhou, Y. *Org. Lett.* **2002**, *4*, 2715−2717 and references therein.

(7) Steroids Catalog, 12th ed.; Q3720-000 (CAS: 66289-21-2), US15/gm.

(8) Recovered alcohol was converted to its 3,5-dinitrobenzoic ester and then subjected HPLC analysis by using OD chiralcel chiral column (*n*-hexane/isopropanol = 99:1; flow rate = 1 mL/min, R_t = 7.52 and 8.38 min).

Table 1. Kinetic Resolution of Various Bishomoallylic Alcohols Using $In(OTf)_3$[a]



entry	1	R	yield (3)[b]	yield (4)[c]	ee (4)
1	**a**	$BnOCH_2CH_2$	44%	28%	>99%[d] (*S*)
2	**b**	$(CH_3)_2CH$	49%	27%	>99%[d] (*S*)
3	**c**	*c*-C_6H_{11}	47%	22%	>99%[e] (*S*)
4	**d**	Ph	40%	23%	>99%[d] (*S*)
5	**e**	$PhCH_2CH_2$	49%	37%	92%[d] (*S*)

[a] Strem Chemicals, Inc. [b] Purified yield. [c] Resolved alcohol **4** was converted to its corresponding 3,5-dinitrobenzoic ester directly after the reaction. Purified yield. [d] Ee was determined using an OD chiralcel chiral HPLC column. [e] Ee was determined using an AD chiralpak chiral HPLC column.

The stereochemistry of the cyclization product **3** was fully established by a series of spectroscopic analyses, as well as single-crystal X-ray diffraction analysis of **3c** (Figure 1).[9]

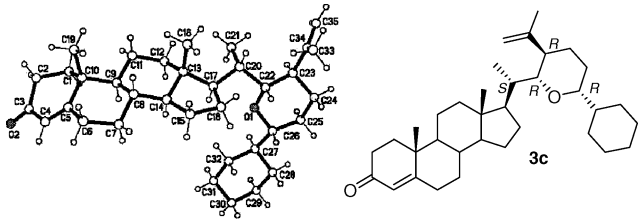


Figure 1. Structure of **3c**.

To rationalize the stereochemical course of this reaction, a transition state assembly was proposed as shown in Figure 2. First, the addition of alkene to oxonium at C-22 followed

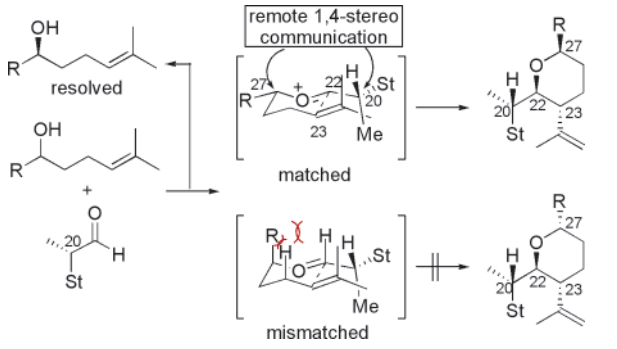
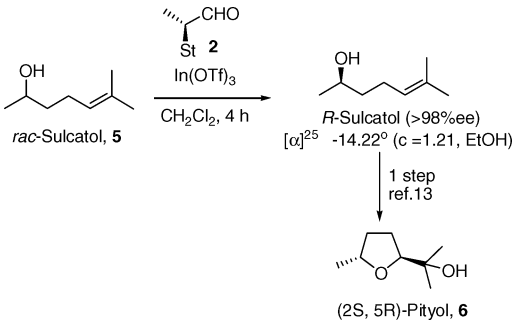


Figure 2. Transition state of the 3,5-oxonium-ene cyclization.

the Cram−Felkin−Anh model.[10,11] Second, the nucleophilic alkene was tethered through a six-membered chair conformation, which set all substituents to be equatorial so as to minimize axial steric interactions. The above two principles posed by this rigid transition assembly nicely linked the chiral center at C-20 to all prochiral centers or the chirality of *rac*-**1**. Thus, the chiral centers at C-22 and C-23 were established via 1,2- and 1,3-stereocontrol. Meanwhile, the remote 1,4-stereocommunication[12] successfully distinguished the chirality of *rac*-**1**, and the highly efficient kinetic resolution was realized. As a result, in a single oxonium-ene reaction, the stereocenter at C-20 of chiral aldehyde substrate **2** determined all three other chiral centers in cyclization product **3**.

Having established the kinetic resolution method and the remote 1,4-stereocontrol mechanism, we examined its applicability and predictability in the synthesis of natural products. Sulcatol **5** is the male-produced aggregation pheromone, which was first isolated from *Gnathotrichus Sulcatus*.[13] Its important biological activity for the insect pest control, together with its biochemical and chemical synthetic relation with another important pest attractant, pityol **6**,[14] stimulated extensive interests in its enantioselective synthesis.[15] By using our kinetic resolution, we successfully resolved the commercially available racemic alcohol in a single step, obtaining (*R*)-sulcatol in 98% ee (Scheme 2).

Scheme 2. Synthesis of (*R*)-Sulcatol



In summary, a remarkable remote 1,4-stereocommunication in $In(OTf)_3$-catalyzed oxonium-ene cyclization was unveiled. On the basis of this stereochemical feature, an efficient kinetic resolution of useful bishomoallylic alcohols was established.[16] Finally, the power of the resolution method was successfully demonstrated in a one-step synthesis of (*R*)-sulcatol with over 98% ee.

Acknowledgment. We are grateful to Singapore Millennium Foundation, Ltd., for a research scholarship to S.L.C. and National University of Singapore for generous financial grants. Thanks are also due to Prof. Koh Lip Lin and Ms. Tan Geok Kheng for the X-ray determination of structure **3c**.

Supporting Information Available: Experimental details, characterization data for all new compounds (PDF) and X-ray crystal data for **3c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) X-ray data for **3c**: Empirical formula $C_{35}H_{54}O_2$; formula weight 506.78; crystal system orthorhombic; space group *P*2(1)2(1)2(1); unit cell dimensions $a = 6.2915(10)$ Å, $b = 16.082(3)$ Å, $c = 30.679$ Å; volume 3104.1(9) Å^3; $Z = 4$; GOF on F^2 1.102; $R_1 = 0.0830$, w$R_2 = 0.1702$.

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(16) Scope and limitation: (1) A stoichiometric amount of chiral source is required. (2) Due to the limitation of the chiral source, only one enantiomer of the bishomoallylic alcohol is obtained. Currently, we are searching for other suitable chiral aldehydes for the kinetic resolution.