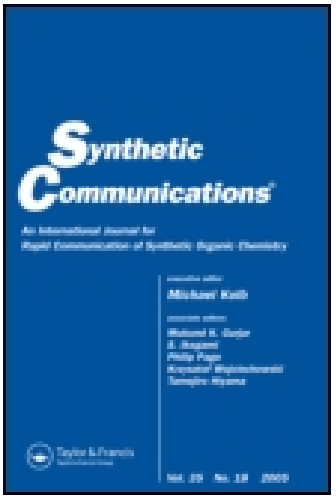

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Asymmetric Synthesis of Octahydrobenzofuran Core Structure with Three Contiguous Stereogenic Centers and Development of the Absolute Configurations

Muhammad Sohail [a], Yao-Feng Wang [a], Shaoxiang Wu [a], Wei Zeng [a] & Fu-Xue Chen [a]

[a] Department of Applied Chemistry, School of Chemical Engineering and the Environment, Beijing Institute of Technology, Beijing, China

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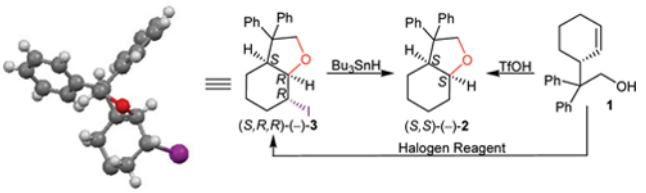
ASYMMETRIC SYNTHESIS OF OCTAHYDROBENZOFURAN CORE STRUCTURE WITH THREE CONTIGUOUS STEREOGENIC CENTERS AND DEVELOPMENT OF THE ABSOLUTE CONFIGURATIONS

Muhammad Sohail, Yao-Feng Wang, Shaoxiang Wu, Wei Zeng, and Fu-Xue Chen

Department of Applied Chemistry, School of Chemical Engineering and the Environment, Beijing Institute of Technology, Beijing, China

GRAPHICAL ABSTRACT



Abstract *Cyclization of enantiopure (S/R)-**1** with halogen-reagent-constructed enantiopure octahydrobenzofuran core structure with contiguous three stereogenic centers of both enantiomers (SRR and RSS). The absolute configurations of all compounds have been established from x-ray analysis of the single crystal of (3aS,7aR,7R)-**3**. The chiral initiation in diastereoselective mode of 5-exo ring closure across C=C bond of pendant cyclohexene moiety has been proposed.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Asymmetric synthesis; heterocyclic; octahydrobenzofuran; stereoselectivity

INTRODUCTION

Development of new and stereospecific organic reactions is a goal for synthetic chemists.[1] Tetrahydrofuran derivatives are well known versatile precursors for the construction of a variety of natural products and therapeutic drugs. Hence, the synthesis of these compounds and their analogs has received increasing research interests.[2] Previously, octahydrobenzofurans, the core structure of many drugs[3]

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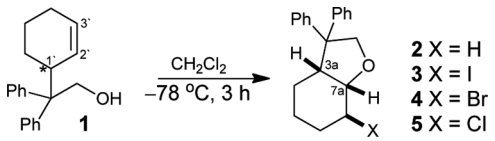
Address correspondence to Fu-Xue Chen, Department of Applied Chemistry, School of Chemical Engineering and the Environment, Beijing Institute of Technology, 5 South Zhongguancun Street, Haidian District, Beijing 100081, China. E-mail: fuxue.chen@bit.edu.cn

and natural products,[4] were synthesized (with single to multistep) by free radical reactions,[5] reduction,[6] tandem conjugate addition,[7] base-catalyzed cyclization,[8] and acid and photochemical rearrangement[9] as the key steps.[10] However, all these compounds were obtained in *racemic* mixture. Although preparative and mechanistic detail of 5-*exo* ring closure across C=C bond of cyclohexene with exclusive formation of *anti*-addition product has been reported recently,[11] the asymmetric synthesis still remains challenging. Herein, we report our construction of the core structure octahydrobenzofuran with excellent diastereo- and enantioselectivity from discrete cycloalkenylalcohol under mild reaction conditions.

RESULTS AND DISCUSSION

We have targeted the chiral center at the C-1′ position of cyclic γ-alkenyl alcohol **1**. In this regard, the starting material **1** was synthesized and resoluted by spontaneous resolution.[12] Each enantiomer was obtained in crystal with optical purity >99% *ee* from *n*-hexane. To evaluate the mode of chiral induction in this type of cyclization, initially, discrete (*S*)-(−)-**1** was treated with a catalytic amount of TfOH in CH_2Cl_2,[13] resulting in the exclusive formation of 5-*exo*-ring closure product (3a*S*,7a*S*)-(−)-**2** (Table 1, entry 1). As expected, the extremely opposite enantiomer (3a*R*,7a*R*)-(+)-**2** was produced with the opposite starting material (*R*)-(+)-**1** (Table 1, entry 2). The chiral center at C-1′ is the origin of this selectivity through 1,2-chiral induction. Keeping in view this observation, we extended our study and sought to gain additional information regarding the selectivity at C-3′. Possible approaches for the facile formation of C-X bond were examined which delivered the desired stereoutcome in high efficiency.

Table 1. Chiral induction in 5-*exo* ring closure across C=C bond of pendant *c*-hexene[a]



Entry	Substrate	Halogen reagent	Product	Yield (%)	*ee* (%)[b]
1[c]	(*S*)-(−)-**1**	—	(3a*S*,7a*S*)-(−)-**2**	100	>99.9
2[c]	(*R*)-(+)-**1**	—	(3a*R*,7a*R*)-(+)-**2**	100	>99.9
3	(*S*)-(−)-**1**	NIS	(3a*S*,7a*R*,7*R*)-(−)-**3**	99	>99.9
4	(*R*)-(+)-**1**	NIS	(3a*R*,7a*S*,7*S*)-(+)-**3**	99	>99.9
5	(*R*)-(+)-**1**	NBS	(3a*R*,7a*S*,7*S*)-(+)-**4**	84	>99.9
6	(*R*)-(+)-**1**	NCS	**5**	NR	—
7[d]	(*R*)-(+)-**1**	**6**	(3a*R*,7a*S*,7*S*)-(+)-**5**	70%	>99.9

[a]Reaction conditions: **1** (0.05 mmol), halogen reagent (0.06 mmol, 1.2 equiv), −78 °C, CH_2Cl_2 (0.5 mL), 3 h, argon atmosphere.

[b]Determined by chiral HPLC on AS-H and OD-H.

[c]TfOH (0.005 mmol, 10 mol%), reflux.

[d]**6** is 1,3-dichloro-5,5-dimethylhydantoin.

Notes. NIS, *N*-iodosuccinimide; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide.

To solve the desired ambiguity, *N*-iodosuccinimide (NIS) was chosen as the model halogen reagent, which worked effectively in the absence of any catalyst. Good yield of haloetherification product (*3aS*,7a*R*,7*R*)-**3** was obtained in CH_2Cl_2 at $-78\,^{\circ}C$ (Table 1, entry 3). As anticipated, the opposite asymmetric induction was observed with the opposite enantiomer (Table 1, entry 4 vs 3). The analytical data of ^1H NMR, ^{13}C NMR, nuclear Overhauser effect spectrometry (NOESY), and high-resolution mass spectrometry (HRMS) confirmed the cyclized product as a single diastereoisomer. When closely observing ^1H NMR of **4**, the upfield doublet of doublets of C-7a proton at 4.38 ppm with $Jae = 4.1$ Hz and $Jaa = 7.5$ Hz and triplet of C-7 proton at 4.42 ppm with $Jae = 4.1$ Hz, and space interaction of proton in NOESY do not furnish a valuable clue about the stereochemistry of **3** at the ring juncture. Fortunately, single-crystal x-ray analysis of (−)-**3** has revealed a *cis*-fused chair conformation of cyclohexane with an axial iodine substituent and defined its absolute configuration as (3a*S*,7a*R*,7*R*) (Fig. 1).

Subsequently, the absolute configurations of **2** and **1** were established on the basis of (*3aS*,7a*R*,7*R*)-**3**. Therefore, dehalogenation of (*3aS*,7a*R*,7*R*)-**3** was accomplished by reduction with Bu_3SnH in toluene at 80 °C yielding (*3aS*,7a*S*)-**2** in 100% yield (Scheme 1). This dehalogenated product (3a*S*,7a*S*)-**2** has the same retention time on chiral high-performance liquid chromatography (HPLC) spectra and rotation value with (−)-**2** prepared by TfOH-catalyzed cyclization of (−)-**1** (Table 1, entry 1), confirming the absolute configuration of cyclized product (−)-**2** as (3a*S*,7a*S*) and the starting material (−)-**1** as (*S*). To the best of our knowledge, this is the first report of highly enantioselective and diastereoselective cycloetherification and cyclohaloetherification of cyclic alkenol.

Under optimized reaction conditions, enantiopure bromide **4** was obtained in good yield as single diastereoisomer from *N*-bromosuccinimide (NBS) (Table 1, entry 5). While no reaction occurred with *N*-chlorosuccinimide (NCS) after 24 h even at room temperature, moderate yield of chloro product **5** was obtained with active 1,3-dichloro-5,5-dimethylhydantoin **6** (Table 1, entry 7). Introduction of halogens make this reaction more unique, exotic, and useful because of the fascinating versatility of chiral halides for many chemical transformations.[14]

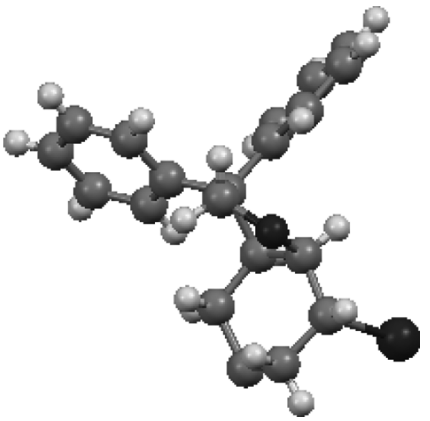
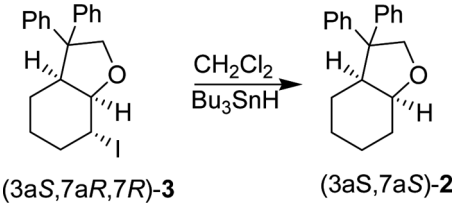


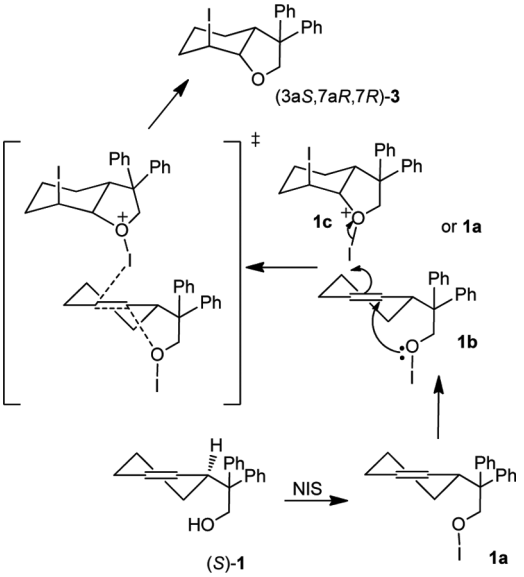
Figure 1. Single-crystal structure of (*3aS*,7a*R*,7*R*)-3.



Scheme 1. Deiodination of (*3aS*,7a*R*,7*R*)-3 by Bu_3SnH.

Finally, the mechanism of this highly diastereoselective reaction has been hypothesized as follows. Intramolecular haloetherificatoin of **1** occurred in a concerted *5-Trig-exo* closing way. First, the activation of alcoholic substrate by NIS (e.g., to form hypoiodite **1a**), is followed by intermolecular iodine transfer from in situ–generated hypoiodite **1a** or **1c** species at C3′ position. This transfer occurs at the C3′β-*Si* face of C=C of cyclohexene moiety. This relocation coupled with an intramolecular *anti* addition of the pendant alcoholic oxygen to alkenyl of C2′α-*Re* face at C2′ results in this 100% diastero- and enantiomerically pure (*3*a*S*,7a*R*,7*R*)-**3** (Scheme 2). Similarly, iodine transfer at C3′β-*Re* face of C=C of *c*-hexene moiety in (*R*)-**1** and the opposite enantiomer (*3aR*,7a*S*,7*S*)-**3** was obtained.

In conclusion, an efficient and convenient route has been developed for the asymmetric synthesis of optically pure octahydrobenzofurans with three contiguous chiral centers, where the stereospecific ring closure reaction can be applied in the total synthesis of imperative molecule. The chiral center at C-1′ is not only incorporated into the ring system but also serves to control the stereochemistry of the rest



Scheme 2. Proposed reaction mechanism of cylohaloetherification.

stereogenic centers. The absolute configurations of all compounds have been established on the basis of x-ray analysis of a single crystal. Further investigations should be focused on application of this method to the asymmetric synthesis of some interesting compounds.

EXPERIMENTAL

HRMS was recorded on a Bruker Apex IV FTMS. Enantiomeric excesses were determined by chiral HPLC on a Shimadzu LC-20A apparatus with Chiralpak AS-H and OD-H. ^{1}H NMR spectra were recorded on a Bruker Avance 600 and Varian Mercury 400. ^{13}C NMR was recorded on a Varian Mercury 400 (100 MHz) with complete proton decoupling. Optical rotations were measured on a Krüss P8000 polarimeter in CH_2Cl_2.

Synthesis of Enantiopure (3a*S*,7a*R*,7*R*)-3

NIS (13.5 mg, 0.06 mmol, 1.2 equiv) was added to a solution of alcohol (*S*)-**1** (13.9 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at − 78 °C. The reaction mixture was stirred at − 78 °C for 2.5 h. After reaction completion, as monitored by thin-layer chromatography (TLC), the crude product was directly loaded on column and purified by flash column chromatography (silica gel, 200–300 mesh; Et_2O–petroleum ether, 1:40, v/v) to give white transparent crystals (20 mg, 99%). Mp 104–105 °C (from *n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.36$ (d, $J = 7.5$ Hz, 2H, Ph-H), 7.29 (d, $J = 7.5$ Hz, 2H, Ph-H), 7.28–7.23 (m, 2H, Ph-H), 7.17–7.13 (m, 4H, Ph-H), 4.77 (d, $J = 8.2$ Hz, 1H, 2-H_a), 4.66 (d, $J = 8.2$ Hz, 1H, 2-H_b), 4.56–4.53 (m, 2H, 7/7a-H), 3.38–3.35(m, 1H, 3a-H), 1.90–1.87 (m, 1H, 6a-H), 1.82–1.76 (m, 1H, 6b-H), 1.72–1.64 (m, 2H, 5-H), 1.38–1.36 (m, 1H, 4a-H), 1.16–1.13 (m, 1H, 4b-H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 145.8$, 143.4, 128.8, 128.4, 128.1, 126.8, 126.5, 126.3, 82.5, 76.3, 58.8, 41.2, 33.2, 30.5, 25.0, 21.5. HRMS calcd. for $C_{20}H_{21}IO$: 427.0529 $(M+Na)^+$, found: 427.0534. Both enantiomers were recognized by chiral HPLC on OD-H (*n*-hexane/*i*-propanol = 90/10, V/V, 1.0 mL min^{-1}, 254 nm), $t_{RSS} = 5.54$ min, $t_{SRR} = 9.97$ min; $[\alpha]_D^{28} = -126.6$ ($c = 0.15$, CH_2Cl_2 for (3a*S*,7a*R*,7*R*)-**3**).

Crystal Data for (3*as*,7a*r*,7*r*)-3 ($C_{20}H_{21}IO$)

$M = 403.76$, momoclinic, *P2(1)*, $a = 6.1252(10)$, $b = 22.600(4)$, $c = 24.191(4)$Å, $\beta = 90.067(2)°$, $Z = 8$. Reflections collected/unique 29745/16218, $R_{int} = 0.0424$, $R_1 = 0.0616$, $wR_2 = 0.1370$ for ($I > 2\sigma(I)$, $R_1 = 0.0720$, $wR_2 = 0.1434$. For details, see CCDC 903689.

SUPPORTING INFORMATION

Experimental procedures, ^{1}H and ^{13}C NMR spectra, HPLC spectra, and x-ray analysis can be found via the Supplementary Content section of this article's Web page.

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