Pergamon

Tetrahedron Letters 40 (1999) 6817–6820

TETRAHEDRON LETTERS

Selective cleavage of the trisubstituted cyclopropanes via cyclopropylcarbinyl radical fragmentation

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Received 10 June 1999; revised 5 July 1999; accepted 9 July 1999

Abstract

The fragmentation reaction of the optically pure 2-aryl-3-alkylcyclopropylcarbinyl radicals **1** proceeded selectively to generate a benzyl radical and produce the optically pure 4-aryl-3-alkyl-1-butenes **2**, which can serve as synthetically useful chiral building blocks.

Keywords: radicals; radical reactions; cyclopropanes; enzymes; enzyme reactions; lignans.

Ring opening reactions of cyclopropanes[1] triggered by cyclopropylcarbinyl radicals have been well known as a method for cleaving carbon–carbon single bonds. While extensive work on cyclopropylcarbinyl radicals has forcused mainly on kinetic studies,[2] only a few examples of reactions from the synthetic point of view have thus far been reported. In particular, systematic investigations of fragmentation reactions of substituted cyclopropylcarbinyl radicals have yet to appear in the literature. We were therefore interested in developing selective fragmentation reactions generated by cyclopropylcarbinyl radicals as a versatile synthetic methodology. We envisioned: (i) that the optically active 2-aryl-3-alkylcyclopropylcarbinyl radicals **1** would give the non-racemic 4-aryl-3-alkyl-1-butenes via the stabilized benzyl radical intermediate **2**[3] (route **a**) rather than via the isomeric alkenes **2′**; and (ii) that if a radical leaving group (e.g., SPh) is introduced as Y, the two reaction processes, i.e., the reaction via route **a** and the tandem C–C bond cleavage/elimination reaction via route **b**, would compete to yield **2** and/or the σ-symmetrical 3-aryl-1,4-pentadienes **3** (Scheme 1). Herein we report a highly enantioselective synthesis of 4-aryl-3-alkyl-1-butenes, via the fragmentation reaction of **1**, which contain three chemically distinguishable functionalities and which can serve as useful chiral building blocks for the construction of a wide variety of biologically active molecules.

The substrates for the radical reaction were prepared from the acetoacetates $\mathbf{4_{ab}}$, which were derived from the corresponding cinnamyl alcohols by transesterification with ethyl acetoacetate. Treatment of $\mathbf{4_{ab}}$ with tosyl azide produced the diazo esters $\mathbf{5_{ab}}$, which were subjected to the Cu-catalyzed

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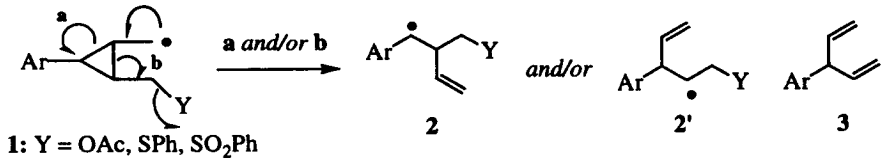
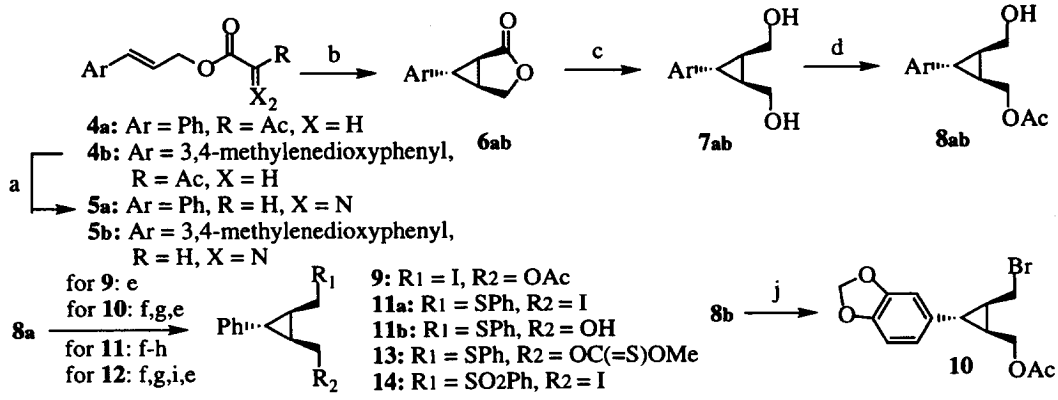
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01366-0



Scheme 1.

cyclopropanation.[4] The resulting bicyclic lactones $\mathbf{6_{ab}}$ were reduced with $LiAlH_4$ to give the diols $\mathbf{7_{ab}}$ diastereoselectively.[5]

We then explored the optimum conditions for desymmetrization of σ-symmetrical diols $\mathbf{7_{ab}}$ using a wide variety of enzymes.[6] Of these, lipase AK, derived from *Pseudomonas fluorescens*, proved to be the best choice in mediating transesterification using vinyl acetate as an acetyl donor in benzene at room temperature. The optically active esters $\mathbf{8_{ab}}$ were obtained in 97% yield,[7] with enantiomeric excesses over 99% as determined by HPLC on Chiralcel OB and OD columns. The absolute stereochemistry of $\mathbf{8_a}$ was established as that shown in Scheme 2 using the PGME method[8] developed by Kusumi.[9] The optically pure alcohols $\mathbf{8_{ab}}$ thus obtained were converted into the corresponding iodide **9** and bromide **10** in 93% and 85% yields, respectively.

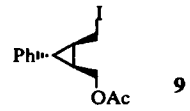
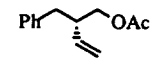
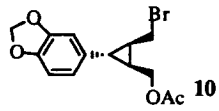
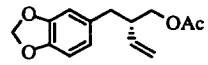
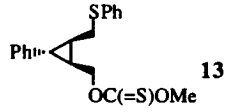
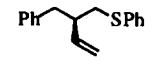
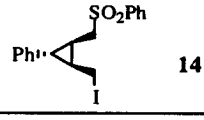
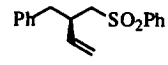


Scheme 2. Reagents and conditions: a, *p*-TsN_3, aq. NaOH, $^nBu_4NBr$, CH_2Cl_2, rt; b, $CuSO_4$, $Cu(acac)_2$, benzene, reflux; c, $LiAlH_4$, THF, rt; d, lipase AK, vinyl acetate, benzene, rt; e, I_2, Ph_3P, imidazole, benzene, rt; f, PhSSPh, $^nBu_3P$, pyridine, rt; g, KOH, aq. EtOH; h, $(imid)_2C{=}S$, MeOH; i, *m*CPBA, $KHCO_3$, CH_2Cl_2; j, CBr_4, Ph_3P, CH_2Cl_2

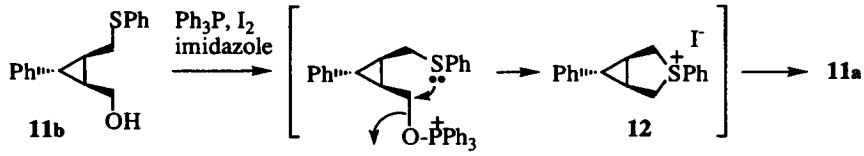
We then examined the radical reaction of **9** and **10**. When the iodide **9** was subjected to standard conditions, the fragmentation reaction proceeded smoothly and the alkenyl acetate $\mathbf{15_a}$ was obtained as a single product in 94% yield (Table 1). In like manner, the bromide **10** was also converted cleanly under the same reaction conditions into $\mathbf{15_b}$ in 92% yield. As we had predicted, these compounds were produced via selective C–C bond cleavage to generate a stabilized benzyl radical. The optical purities of both $\mathbf{15_{ab}}$ were determined to be over 99% ee, which indicated that the chirality of the starting cyclopropanes was completely retained during fragmentation. We next examined the radical reaction of **11a**,[10] which contains a radical leaving group (SPh) and which therefore has the possibility of competitive reactions, as shown in Scheme 1. In this instance, the product was the alkenyl sulfide **16**, obtained following the same procedure as for **9** and **10**; however, its optical purity was surprisingly low (14% ee). Presumably racemization occurred in the iodination of the alcohol $\mathbf{11_b}$ via the sulfonium intermediate **12**, as shown in Scheme 3.

To prove our hypothesis, the thiocarbonate **13** was prepared and subjected to the radical reaction to give the same sulfide **16**, whose ee was >99%, thus clearly confirming the mechanism. Furthermore,

Table 1
Radical reaction of the cyclopropane derivatives[a]

entry	substrate	reaction time (h)	product	yield (%)	ee (%)
1	 **9**	1.5	 **15a**	94	>99
2	 **10**	2	 **15b**	92	>99
3	 **13**	8	 **16**	76	>99
4	 **14**	4	 **17**	88	>99

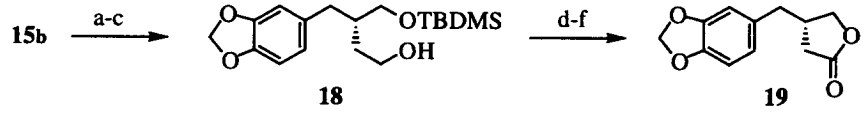
[a]The reaction was conducted in the presence of tri-n-butyltin hydride (0.02 M, 2 eq.) and 2,2'-azoisobutyronitrile (0.01 eq.) in refluxing benzene solution.



Scheme 3.

the fact that the reaction of the sulfone **14** yielded the alkenyl sulfone **17** with >99% ee also supports this premise. From these experiments, it was demonstrated that in competitive reactions, the C–C bond cleavage to generate a benzyl radical also predominates, producing the optically pure 4-aryl-3-alkyl-1-butenes selectively.

To demonstrate the versatility of the fragmentation products, the optically pure $\mathbf{15_b}$ was converted into a key common intermediate **19** for the synthesis of biologically significant lignans[11] (Scheme 4). Sequential hydrolysis, silylation and hydroboration of $\mathbf{15_b}$ provided the alcohol **18**, which was oxidized, deprotected and treated with acidic conditions to produce the lactone **19** in reasonable overall yield, the spectral properties and optical rotation of which were completely identical with those reported in the literature.[11]



Scheme 4. Reagents and conditions: a, KOH, aq. KOH; b, ^{t}BuMe$_2$SiCl, imidazole, 4-DMAP, DMF, rt, 92% (two steps); c, 9-BBN, THF, rt then NaOH, H_2O_2, rt, 98%; d, Dess–Martin periodinane, CH_2Cl_2, rt, 94%; e, $NaClO_2$, NH_2SO_3H, aq. ^{t}BuOH, rt; f, *p*-TsOH (cat.), CH_2Cl_2, rt, 60% (three steps)

In conclusion, we have demonstrated that the fragmentation reaction of optically pure trisubstituted cyclopropylcarbinyl radicals, generated via a lipase-mediated desymmetrization of the σ-symmetrical diols, produced the 4-aryl-3-alkyl-1-butenes enantioselectively, the synthetic usefulness of which has

been demonstrated by an application to the synthesis of a key intermediate for lignans. The synthetic methodology developed here holds considerable promise for the synthesis of other optically active biologically significant molecules.

Acknowledgements

We are grateful to Dr. Yoshihiko Hirose, Amano Pharmaceutical Co., Ltd., for providing lipase AK. We also thank Professor Ilhyong Ryu, Osaka University, for valuable discussions.

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5. The stereochemistry was confirmed by a NOESY experiment of **14′** (R_1=SO_2Ph, R_2=OH).
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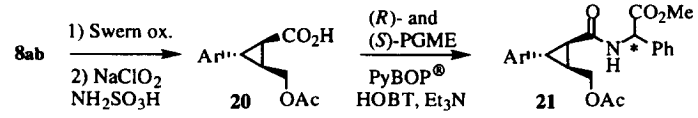
8. The alcohol **8a** was transformed to the acid **20**, which was condensed with (*R*)- and (*S*)-phenylglycine methyl ester (PGME) to give the corresponding amides $\mathbf{21}_R$ and $\mathbf{21}_S$ as shown below. The absolute configuration was determined by $\Delta\delta$ values ($\Delta\delta=\delta_S-\delta_R$) of the protons.



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