Oxygen Atom Insertion into the Benzylic Carbon-Hydrogen Bond of (*R*)-(−)-2-Phenylbutane by Methyl(trifluoromethyl)dioxirane: An Efficient and Mild Regio- and Stereoselective Synthesis of (*S*)-(−)-2-Phenyl-2-butanol

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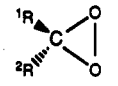
Received July 29, 1991

The efficient conversion of (*R*)-(−)-2-phenylbutane [(−)-1] into (*S*)-(−)-2-phenyl-2-butanol [(−)-2] with high configurational retention was achieved under remarkably mild conditions by using methyl(trifluoromethyl)dioxirane (3a). The Arrhenius activation parameters were determined by using methyl(trifluoromethyl)dioxirane (3a) in solution of 1,1,1-trifluoropropanone (TFP) or methylene chloride. A significantly lower activation energy was determined for the oxyfunctionalization of (±)-1 by 3a in the less polar methylene chloride. An ordered transition state I is proposed for this regio- and stereoselective O atom insertion into the benzylic C–H bond of hydrocarbon (−)-1.

Introduction

The oxyfunctionalization of unactivated C–H bonds in saturated hydrocarbons is one of the most important challenges for synthetic organic chemists.[1] The difficulty consists in achieving selective oxidations that are successfully performed by biological systems (e.g., cytochrome P-450 enzymes).[2] Dioxiranes, used either in situ[3] or in isolated form,[4] have in recent years been used intensively as oxidants in synthetic work.[5] The most remarkable application is the efficient and selective O atom insertion into unactivated C–H bonds of alkanes.[6] Compound 3a is an oxidant much more powerful than 3b, and its use at low temperature has allowed the achievement of the oxyfunctionalization of a variety of saturated hydrocarbons.[6b]



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(3a : ^{1}R=CF$_3$, ^{2}R=CH$_3$; 3b : ^{1}R=^{2}R=CH$_3$)

Little has been reported[7] on the oxidation of tertiary C–H bonds of optically active alkanes to the corresponding optically active tertiary alcohols. Reactions with chromic acid[7a] and permanganate[7b] occur with predominant retention of configuration, but the low yields limit the scope of these reactions as synthetic methods. Dry ozonation[7c] appears to be promising to obtain optically active tertiary alcohols from optically active hydrocarbons, but enantiomeric excesses of ca. 80% were obtained at best.

Despite the much higher reactivity (up to several thousands times) of the fluorinated derivative 3a compared to dimethyldioxirane 3b, remarkable regio- and stereoselectivities have been found for preferential attack at tertiary versus secondary C–H bonds. For example, hydroxylations of *cis*- and *trans*-decalin and *cis*- and *trans*-1,2-dimethylcyclohexane were found to proceed in a high degree of retention of configuration. Furthermore, optically active silanes are efficiently converted into the configurationally retained silanols by using 3a,b in a solution of the corresponding ketones.[8]

Results and Discussion

We now report on the oxidation of the optically active hydrocarbon[9,10] (*R*)-(−)-2-phenylbutane [(−)-1] by 3a. The oxidation of (−)-1 (72% optically pure, see Experimental Section) with 3a in 1,1,1-trifluoropropanone (TFP) or ketone-free methylene chloride solutions[11] led to (*S*)-(−)-2-phenyl-2-butanol [(−)-2][12] in ca. 95% yield. ^{1}H NMR analysis[13] by using (+)-Eu(hfbc)$_3$ permitted us to establish that the alcohol (−)-2 was 72% optically pure; therefore, the oxidation proceeds with complete retention of configuration. The hydroxylation procedure simply involves addition of a cold aliquot of a standardized solution of either dioxirane 3a in TFP or ketone-free 3a in CH_2Cl_2 to the hydrocarbon (−)-1 dissolved in TFP or CH_2Cl_2 and

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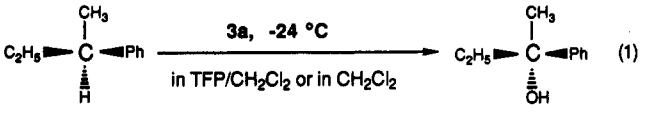
Table I. Rate Constants and Activation Parameters for the Oxidation of 2-Phenylbutane [(±)-1] by Methyl(trifluoromethyl)dioxirane (3a)

solvent	T (°C)	$10^2 \times k_2$[a] (M^{-1} s^{-1})	E_a[b] (kcal mol^{-1})	log A[b]	$\Delta S^{\ddagger}$[b,c] (cal mol^{-1} K^{-1})
CH_2Cl_2	-15.0	2.83			
CH_2Cl_2	0.0	7.34	9.7 ● 0.2	6.6 ● 0.2	-30 ± 2[d]
CH_2Cl_2	9.9	15.10			
TFP	-19.8	0.55			
TFP	0.0	2.58	11.3 ± 0.2	7.4 ± 0.2	-26 ± 2[e]
TFP	9.7	5.82			

[a] Second-order rate constant k_2 were calculated as $(k_1/[3a]_0)$; k_1 values (s^{-1}) were obtained from pseudo-first-order kinetics with $[1]_0$ = 0.02–0.03 M; rate constants k_1 were obtained from two or more independent runs which agreed within ±5%. [b] As estimated from a log k_2 versus [(1/T), K^{-1}] plot; standard errors shown. [c] Calculated at 0 °C. [d] $\Delta G^{\ddagger}$ = 17.4 kcal mol^{-1} calculated at 0 °C. [e] $\Delta G^{\ddagger}$ = 17.9 kcal mol^{-1} calculated at 0 °C.

recovery of the product upon removal of the solvent in vacuo.



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The efficiency displayed by dioxirane **3a** in the oxyfunctionalization of (–)-1 is unmatched by dimethyldioxirane **3b**. For example, an over 10-fold excess of dimethyldioxirane (**3b**) was necessary to obtain a 50% conversion of (–)-1 at 25 °C after 2 days. By contrast, almost total conversion of (–)-1 into (–)-2 was obtained by using only a 2-fold excess of dioxirane **3a** at –24 °C during 1 h. No products derived from the attack of dioxirane **3a** on secondary C–H bonds were detected, which confirms the high regioselectivity for tertiary C–H bonds in the oxyfunctionalization by dioxirane **3a**.

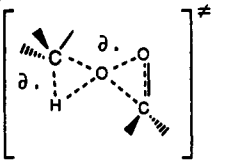
The success of obtaining dioxirane **3a** as a ketone-free solution, e.g., in methylene chloride, by water extraction of the TFP,[11] has allowed us for the first time to determine the influence of the solvent on the rate of O atom insertion into a C–H bond of a hydrocarbon. For this purpose we measured the rate of oxidation of the racemic hydrocarbon (±)-1 at three different temperatures by ketone-free **3a** in methylene chloride and by **3a** in TFP; the kinetic parameters are given in Table I.

The oxidations were found to obey second-order kinetics (first order each in dioxirane and in substrate), which yielded integrated second-order rate plots that were linear to over 80% substrate conversion. A significantly lower activation energy value was found for the oxidation of (±)-1 by dioxirane **3a** in the less polar methylene chloride (see Table I).

Large and negative values were found for the activation entropy in both methylene chloride and TFP solutions, suggesting that a change in solvent polarity has little effect on the ordering in the transition state.

The fact that the oxyfunctionalization of the optically active hydrocarbon (–)-1 by dioxirane **3a** occured with complete retention of configuration and the large and negative activation entropy values, suggest a mechanism which involves the highly ordered transition state I analogous to that proposed for other stereoselective hydroxylations.[6a,b,8]

In view of the weak peroxide bond in dioxiranes, the transition state I might have appreciable diradical character; however, the formation of a pair of separate radicals can be rejected on the basis of the observed complete retention of configuration. Furthermore, the lack of



I

products derived from radical reactions, or even arising from the radical-initiated chain decomposition of dioxirane **3a** itself,[11] corroborate that discrete free radicals are not involved in this O atom insertion.

The lower activation energy in the less polar methylene chloride strongly suggests the absence of significant charge separation on going from ground to transition state in this reaction. A decrease of the reaction rate in the more polar TFP would be expected for a transition state with diradical character such as I, which signifies a decrease of dipolar character in going from the more polar dioxirane **3a** to the less polar transition state I. Such a solvent effect had been already observed in oxidation reactions carried out by dimethyldioxirane (**3b**).[5b]

In summary, although a number of recent hydroxylation methods[14] permit the O atom insertion into unactivated C–H bonds of hydrocarbons, regio- and stereoselective hydroxylations are rare.[1] For such cases the dioxirane **3a** represents the reagent of choice in synthetic chemistry. Employing ketone-free dioxirane **3a**, we could unveil a sizeable solvent effect on rates of O insertion; this is particularly interesting since we have recently reported[11] that the radical chain decomposition of the same dioxirane is not appreciably solvent dependent.

Experimental Section

^1H NMR and ^{13}C NMR spectra were obtained by using a Brucker AC 200 spectrometer. IR spectra were recorded on a Perkin-Elmer 1420 instrument. GLC analyses were performed on a Fractovap 4100 (Carlo Erba) or on a KNK 3000-HRGC (Konik) instrument equipped with a BP5 capillary column (50 m, film thickness 0.25 μm, i.d. 0.22 mm).

1,1,1-Trifluoro-2-propanone (TFP) (Fluka) and Caroate triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (a gift from Degussa AG, Hanau, Germany) were employed in the preparation of TFP solutions of methyl(trifluoromethyl)dioxirane (**3a**) according to a described protocol.[6b] Ketone-free solutions of **3a** in CH_2Cl_2 were obtained by following the procedure recently reported.[11] Dimethyldioxirane (**3b**) solutions in acetone (ca. 0.1 M) were prepared by the standard reported procedure.[4b,c]

(*R*)-(–)-2-Phenylbutane [(–)-1] (bp 60–61 °C/20 Torr; $[\alpha]^{25}$ = –17.5° (neat) (lit.[10] $[\alpha]^{25}$ = –24.3° (neat), ee 72%)) was prepared in 70% yield by Ni-Raney hydrogenation of (*R*)-(–)-3-phenyl-1-butene ($[\alpha]^{22}$ = –4.69° (neat) (lit.[9] $[\alpha]^{22}$ = –6.39° (neat), ee 73.4%)) in EtOH solution.[9]

(*S*)-(–)-2-Phenyl-2-butanol [(–)-2]. In a typical procedure, 0.44 g (3.3 mmol) of (–)-1 were dissolved in TFP (10 mL) or CH_2Cl_2 (20 mL) and the resulting solution was cooled down to –24 °C; a 2-fold excess of dioxirane **3a** in TFP or CH_2Cl_2 (concentrations ranging between 0.7 to 1.0 M, standardized by iodometry) was added at once keeping the temperature at –24 °C. After 1 h, GC monitoring established the total conversion of (–)-1. The solvent was removed under vacuum and column chromatography (silica gel, *n*-hexane/ether (7:3)) afforded 0.47 g of the pure alcohol (95% yield) as a colorless liquid. ^1H NMR (200 MHz) by using (+)-Eu(hfc)$_3$ (Aldrich) in a mixture $DCCl_3/CCl_4$ (50:50) showed that this material was 72% enantiomerically pure. The spectral data of alcohol (–)-2 were in agreement with those reported.[12] The same experimental method was used for the oxidation of (–)-1 by dioxirane **3b** in acetone/CH_2Cl_2 solutions. By using a 10-fold

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excess of **3b** at 25 °C, after 2 days 50% conversion of (-)-1 (GC monitoring) was achieved and (-)-2 was isolated in 30% yield.

The kinetic measurements were performed by following the procedure reported previously;[6b] the results are given in Table I.

Acknowledgment. This work was supported in part by the Deutsche Forschungsgemeinschaft (SFB No. 347 "Selective Reaktionen Metall-aktivierter Molekule"), the Fonds der Chemischen Industrie, the Spanish Dirección General de Investigación Científica y Técnica (PB87-0989), and the Italian Ministery for University and Scientific Research (MURST 40). We thank the A. von Humboldt Foundation (R.M. and M.E.G.-N.) and the Spanish Ministerio de Educación y Ciencia (R.M.) for postdoctoral fellowships. A generous gift of (*R*)-(-)-3-phenyl-1-butene was supplied by Prof. G. Wilke, Max-Planck-Institut für Kohleforschung (Mülheim, Germany), for which we are most grateful.

Registry No. (-)-1, 5787-29-1; (±)-1, 36383-15-0; (-)-2, 53777-08-5; **3a**, 115464-59-0.

Internal Nucleophilic Termination in Biomimetic Acid Mediated Polyene Cyclizations: Stereochemical and Mechanistic Implications. Synthesis of (±)-Ambrox and Its Diastereoisomers

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Received June 12, 1991

Treatment of 10 structurally related trienols and dienols **5–8** with an excess of fluorosulfonic acid in 2-nitropropane at -90 °C afforded, in 74–87% yield, diastereoisomeric mixtures of the odoriferous norlabdane oxides **9–15** ((-)-**9** (Ambrox) is a naturally occurring ambergris odorant). These transformations represent examples of efficient biomimetic acid-mediated cyclizations in which the hydroxyl group serves as the internal nucleophilic terminator. The stereochemical outcome of these kinetically controlled processes has been analysed in detail, and mechanistic hypotheses consistent with the results have been proposed. For the four acyclic trienols **5**, the major reaction pathway can be rationalized by a totally synchronous process involving three internal anti additions via chair or skew-boat conformations of the nascent cyclohexane rings. An alternative explanation postulates a nonsynchronous process in which ring closure to an intermediate cyclohexyl cation is followed by rapid cyclization, directed by a strong kinetic preference for equatorial C–C and C–O bond formation. In contrast, for the monocyclic dienols **6–8** only a nonsynchronous process, involving prior protonation of the cyclohexenyl bond, is fully consistent with the results. In the nonsynchronous processes, the orientation of the side chain vicinal to the cyclohexyl cation directs the stereochemical course of the cyclization. For the acyclic trienols, this factor is predetermined by the configuration of the C(7)=C(8) bond, whereas, for the monocyclic dienols, this orientation is determined by the stereoselective axial protonation of the cyclohexenyl bond in **6**, or by the distribution of cyclohexene and cyclohexane conformers in **7** and **8**, respectively. In the cases studied, it is clear that *conformational inversion of the six-membered ring is slower than cyclization* and thus ensures that an equatorial side chain leads to a trans A/B ring junction in the cyclization product, whereas an axial side chain affords a cis A/B ring junction.

Introduction

Despite extensive studies concerning the stereoselective construction of polycyclic systems via the nonenzymatic acid-catalyzed cyclization of polyenes,[1] the preparation of polycyclic ethers in which a hydroxyl group serves as an internal nucleophilic terminator has seldom been reported.[2,3] Our continued interest in stereocontrolled routes to naturally occurring drimanes[4] and norlabdanes[5] encouraged us to investigate the synthetic potential and stereospecificity of this biomimetic transformation. In this context we now present a detailed stereochemical analysis and mechanistic interpretation of the acid-mediated cyclizations of isomeric polyenols **5–8** to tricyclic ethers **9–15**,[6] compounds which have attracted considerable synthetic interest due to their special organoleptic properties.[7]

Results and Discussion

Stereochemically pure samples of homoallylic alcohols **5–8** were conveniently prepared, albeit in modest yield (21–23%), from ketones **1–4** using a Wittig reaction[8] fol-

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(7) Ambrox ((-)-**9**, trade name of Firmenich SA) is a commercially important odorant naturally occurring in ambergris, see: Ohloff, G. In *Fragrance Chemistry*; Theimer, E. T., Ed.; Academic Press: New York, 1982; p 535. For syntheses of (-)-**9** and its racemate, see: Snowden, R. L.; Linder, S. M. *Tetrahedron Lett.* **1991**, *32*, 4119.

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