Mechanistic and Preparative Studies on the Regio- and Stereoselective Paraffin Hydroxylation with Peracids[1]

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Reactions of more than 20 hydrocarbons with *p*-nitro- or, e.g., 3,5-dinitroperbenzoic acid in chloroform show regioselectivities of $R_s^t = 90$ (relative rates of attack at tertiary and secondary C–H bonds, after statistical correction) to 500 and configurational retention, if applicable, of typically 97–99.7%. Radical side reactions are recognized by concomitant formation of, e.g., nitrobenzene and are responsible for a decrease in regio- and stereoselectivity. Steric effects are observed in attack at axial tertiary C–H bonds and at bridgehead positions. Electronegative and hydrogen-bonding substituents in the alkane diminish, and alkyl groups enhance the rates; the observed Taft ρ^* value of −2.2 indicates substantial positive charge accumulation in the transition state in agreement with the high regioselectivity. A Hammett reaction constant of +0.63 is obtained from substituted perbenzoic acids; activation parameters of $\Delta H^* = 15$–19 kcal mol^{-1} and $\Delta S^* = -22$ to −29 eu with three alkanes of different flexibility and an isotope effect of $k_H/k_D = 2.2$ with methylcyclohexane are measured. Aromatic rings are usually not attacked but lead to deactivation of the peracid even at remote alkane C–H positions; similar deactivation is found in hydrogen-bonding solvents. Androstanes yield preferentially 9α- and 5α-hydroxy products, if, e.g., a 17β-acetoxy substituent is used to steer the reaction. Diols usually are only observed as a result of a proximity effect of a peracid associated at the first formed hydroxy group. The results point to relatively late and oxenoid transition states with substantial charge separation in the substrate. Attempts to achieve selective oxidations using macrocyclic azacyclophanes with attached carboxylic functions were not successful, although the host compounds showed selective complexation of hydrocarbons.

Highly selective oxidations of nonactivated C–H bonds in paraffins belong to the few biological processes[2] for which the counterpart of a similar organic reaction is rarely known. Some more recently studied alkane oxidation reactions[3] involve *N*-oxides,[4] oxygen,[5] hydroxy radicals,[6] peroxides,[7] ozone,[8] and porphyrin P-450 models.[9] Hydroxylations of hydrocarbons with nonactivated peracids[3d,10] proceed via hydroxy radicals. The very reactive pertrifluoroacetic acid has been studied as a possible model for enzymatic hydroxylations.[11] The stereoselectivity claimed in a preliminary report[11b] in our hands could not be reproduced; the instability of tertiary alcohols in the presence of trifluoroacetic acid,[11c] which rapidly yields tertiary trifluoroacetates, leads to subsequent cascades of elimination and addition products. Only adamantane shows a clean reaction due to its resistance to elimination at the bridgehead position. The combination of moderately activated peracids with a lipophilic solvent, however, produces tertiary alcohols in reasonable yields with a remarkable retention of configuration.[12] Tertiary alcohols are obtained instead of esters in this simple procedure with

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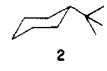
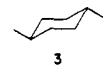
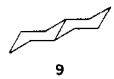
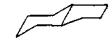
Table I. Hydroxylations with *p*-Nitroperbenzoic Acid. Regio- and Stereoselectivity (R_s^t and % Retention, Respectively) and Relative Rates[a]

	 1	 2	 3	 4
R_s^t	95	*b*	90	100
% ret			95	95
k_{rel}	1.00	1.3	1.05	1.65
	 5	 6	 7	 8
R_s^t	95	*c*	140	140
% ret	100	*c*	97	97
k_{rel}	0.9	0.9	1.05	1.65
	 9	 10	 11	 12
R_s^t	160	190	140	300
% ret	100	99	95	100
k_{rel}	4	6		
	 13	 14	 15	
R_s^t	150	14[d]	60	
% ret			98	
k_{rel}	0.7	0.1		

$H_3CCH(CH_3)CH_2CH_2CH_3$ **16**

R_s^t 13

k_{rel} 0.43

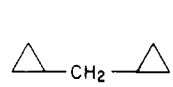
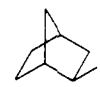
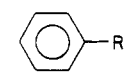
$H_3CCH_2CH(CH_3)CH_2CH_3$ **17**

20

$H_3CCH(CH_3)CH_2CH_2CH(CH_3)CH_3$ **18**[e] → 91%, 2-OH + 9%, 2,5-$(OH)_2$

$H_3CCH(CH_3)CH_2CH_2CH_2{}^*CH(CH_3)CH_2CH_3$ **19a** → 38%, 2-OH; **b** +62%, 6-OH (retention[f])

No reaction detected

($k_{rel} \leq 0.1$) with  **20**  **21**  **22**  **23**

23a, R=H
b, R=$CHMe_2$
c, R=$CHMeCH_2Me$
d, R=CH_2CH_2-cyclohexyl

[a] R_s^t ratio of attack at tertiary to secondary C-H bonds after statistical correction; [error from ±2 to ±20 for R_s^t = 13 to R_s^t = 300; see Table V; attack at primary bonds not detected. Rates relative to 1 ($k = 4.4 \times 10^{-5}$ L mol^{-1} sec^{-1}) per one tertiary C-H bond (after statistical correction). Reaction conditions for kinetic determinations: $CHCl_3$; 60.0 °C; for product studies 5 mmol of hydrocarbon and 5 mmol of peracid in 3-6 mL of $CHCl_3$ under reflux or at 60 °C, alternatively, 6-18 h. Retention in % (±1%); higher selectivities see Table II. [b] Products not analyzed. [c] Not determined. [d] Substantial radical side reaction (recognizable in formation of nitrobenzene). [e] Reaction with 2 mol of peracid. [f] See Experimental Section.

high regio- and stereoselectivity; this result is largely due to the low solubility of the free acids formed from the peracids in hydrophobic solvents, such as chloroform. After our initial report, the reaction, which can be safely scaled up without difficulties, has been applied in the preparation of several tertiary hydroxy compounds.[13] In the present work, we make use of the probably unique opportunity to study the scope and mechanism of a hydroxylation reaction with enzymelike specificity by varying both substrate (Table I) and peracid structure. In dilute solutions the homogeneous reaction mixtures also allowed the kinetics to be followed without difficulties.

Results

A radical side reaction by the known decomposition of peracids[3d,10] leads to lower regio- and stereoselectivity and to a concomitant formation of the corresponding derivative (R–H), such as to nitrobenzene:

$$R\text{–}CO_3H \rightarrow RCO_2\cdot + \cdot OH \rightarrow R\cdot + CO_2 + \cdot OH$$

$$'R\text{–}H + R\cdot \rightarrow 'R\cdot + R\text{–}H$$

$$'R\cdot + R\text{–}CO_3H \rightarrow 'R\text{–}OH + R\text{–}CO_2\cdot \rightarrow \rightarrow$$

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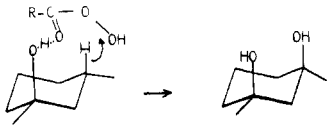
Table II. Hydroxylations with Different Perbenzoic Acids[a]

perbenzoic acid substituent X	methylcyclohexane		1,2-dimethylcyclohexane					
			cis			trans		
	rate	R_s^t	% conv	R_s^t	% ret	% conv	R_s^t	% ret
p-NO_2	10.5	90	52	140	97	48	140	94
m-NO_2[b]	2.5	125						
m-Cl	1.9	38[c,d]	30	100	50[d,e]	58	150	92[f]
m-Cl + I_2[g]			39	250	83[h]	73	180	94
3,5-$(NO_2)_2$	11.2	250	47	>500	99.6			

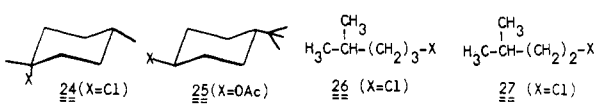
[a] Usual reaction conditions: 5 mmol of peracid and 5 mmol of hydrocarbon in 4 mL of chloroform; 6–12-h reflux; rates relative to perbenzoic acid (X = H, k_{rel} = 1); % conversion by ^{13}C NMR and GLC. Other footnotes regarding R_s^t and ret; see Table I. [b] Measurements at low conversion (from kinetic runs). [c] Byproduct, 25% C_6H_5Cl. [d] Similar results with *trans*-decalin: 83% retention at 53% conversion, 9% C_6H_5Cl. [e] 17% C_6H_5Cl. [f] 20% C_6H_5Cl. [g] I_2, 4×10^{-3} M. [h] 5% C_6H_5Cl.

The radical process is more prominent with less activated peracids, such as *m*-chloroperbenzoic acid (Table II), and with the less reactive acyclic hydrocarbons but can be largely suppressed by addition of iodine as inhibitor (Table II). Although 3,5-dinitroperbenzoic acid shows less side reaction and even higher selectivities (Table II), most experiments were performed with *p*-nitroperbenzoic acid, which is easier to prepare and also yields selectively a large number of tertiary hydroxy compounds (Table I).

Steric, Substituent, and Solvent Effects. With the exception of adamantane (**13**), reactions at bridgehead positions are either undetectable, as in norbornanes (**21**, **22**), or slower, as in bicyclo[2.2.2]octane (**14**), and furthermore show largely radical-type products. Cyclohexanes bearing equatorial tertiary C–H bonds consistently react faster than those with axial C–H bonds. Rate comparisons of the epimers **3**/**4**, **7**/**8**, and **9**/**10** (Table I) show a ratio of $k_{eq\,C-H}/k_{ax\,C-H}$ = 1.9 ± 0.2. *trans*-1,3-dimethylcyclohexane (**6**) is not oxidized faster than its epimer **5** because of additional steric hindrance of axial attack by the second methyl group. *cis*-1,3-Dimethylcyclohexane (**5**) is the *only* cycloalkane that yields substantial amounts of diol; this can be ascribed to a proximity effect of a peracid molecule associated to the first formed hydroxy group:[14]



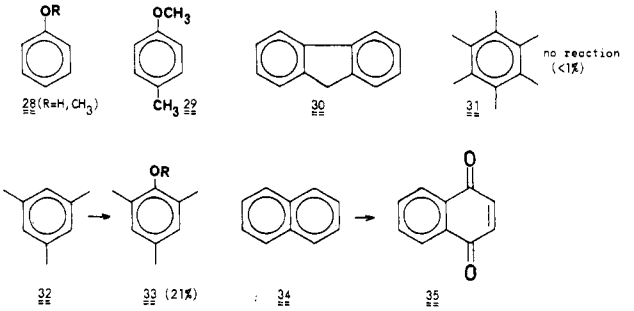
Additional alkyl groups in position β to the tertiary C–H bond enhance the rates significantly, as illustrated by the decalins **9**/**10** and even by the more hindered cyclohexane **2**. Electron-withdrawing substituents even in remote δ-position such as in **24** or **26** (X = Cl) retard the velocity; the effect of γ-substituents (**27**) is expectedly larger (k_{rel} rate constants relative to X = H).



k_{rel} = 0.9 k_{rel} < 0.18 k_{rel} = 0.75 k_{rel} = 0.06

Oxygen-containing substituents showed specific effects (see below); hence, only four derivatives could be used to construct a Taft plot (Figure 1), which, however, clearly indicates a positive charge accumulation in the transition state. The presence of OR groups in the substrate diminishes the rates to a degree that usually prevents the formation of diols if the two tertiary C–H bonds are not too far apart (as in **19**) or if there is no special proximity effect such as with **5** (see above). Acetoxy groups are particularly effective, as demonstrated with **25** as well as by the sharp rate decrease upon addition of ethyl acetate to chloroform even in small concentrations (Table III). Alkoxy substituents usually lead to further oxidation at vicinal positions to the OR groups.[15] All hydrogen-bonding solvents give substantially lower yields in spite of their better ability to dissolve the peracid (Table III). The solvent effects obviously resemble those in the Prileschajev reaction and have their origin in the disruption of the intramolecular hydrogen bond in the percarboxylic group.[16]

Aromatic Compounds. Aromatic nuclei usually are unreactive and even prevent reaction at tertiary C–H bonds that are remote from the π-system (**23a–d**). The only rationalization for this seems to be the action of the benzene ring—or a cyclopropane in **20**—as a hydrogen-bond acceptor, thus deactivating the peracid. Only aromatic compounds with strongly electron-donating substituents show reactions with *p*-nitroperbenzoic acid in chloroform, which are similar to well-known oxidations with pertrifluoroacetic acid.[17] Reactive derivatives such as **28–30** are completely oxidized and yield carbon dioxide. Hexamethylbenzene (**31**) is essentially inert; mesitylene (**32**) and naphthalene (**34**) yield a number of compounds from which **33** and **35** could be assigned as major products.



Steroids. Oxidation of (5α)-androstane with *p*-nitroperbenzoic acid leads to several compounds, from which only an oxo derivative (probably 15-oxo) could be identified; the reaction with the 17β-acetoxy steroids **36**, however, yields the expected mono- and dihydroxylation products, the latter being formed for the same reasons as discussed for the *cis*-1,3-dimethylcyclohexane (**5**). Addition of iodine traces was found necessary to suppress radical side reactions with the steroids. In **36** (R = OAc) the 5α-position is additionally deactivated, whereby only

(14) For a similar proximity effect in epoxidation, see: Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374.

(15) Schneider, H.-J.; Ahlhelm, A.; Müller, W. *Chem. Ber.* **1984**, *117*, 3297.

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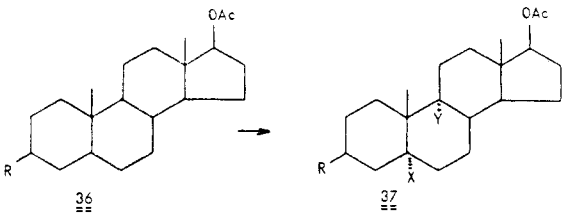
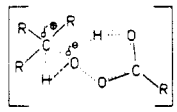
(17) (a) Chambers, R. D.; Goggin, P.; Musgrave, W. K. R. *J. Chem. Soc.* **1959**, 1804. (b) Hart, H. *Acc. Chem. Res.* **1971**, *4*, 337.



mol of RCO_3H/ mol of steroid	R = H 2	R = H 4	R = OAc 4
X = OH; Y = H	15%	14%	
X = H; Y = OH	15%	8%	20%
X = Y = OH		30%	

the 9α-hydroxy product was isolated. The C8–H position is not attacked due to the strong steric hindrance by the angular methyl groups. The results show that, in the presence of several tertiary centers, a more selective reaction, by which, e.g., the androstanediol derivative **37** (X = Y = OH) can be obtained in a single step, can be steered by the introduction of additional substituents such as an acetoxy group.

Further Kinetic Results and Mechanistic Interpretation. The reaction constant $\rho = +0.57$ obtained from a Hammett analysis with substituted perbenzoic acids (Figure 2) is complementary to the Taft ρ^* value of −2.2 observed for the substrate (Figure 1e and indicates a moderately electrophilic nature of the reaction. In olefin epoxidations similar, although larger perbenzoic reaction constants[18] and also similar solvent effects[16] are observed. Another parallel exists in the large negative activation entropy, as measured with compounds **1**, **10**, and **16** (Table IV), which indicates a substantial loss of mobility in the transition state, particularly with the more flexible hydrocarbons *cis*-decalin and 2-methylpentane. The high degree of retention observed with both the epimeric cycloalkanes and the chiral tetrahydrocitronellene (**19**) would also agree with a cyclic transition state as proposed first by Bartlett.[11a,b,19] The remarkable regioselectivity as well as the observed reaction constants would, however, suggest some charge separation in such an oxenoid mechanism, as illustrated below:



The small kinetic isotope effect, which was measured with perdeuteriomethylcyclohexane (Table IV) and therefore represents the sum of primary and secondary effects, is also more indicative of an oxenoid than of a radical or ionic mechanism. Symmetrical transition states, which are typical for many radical substitutions in hydrocarbons, can be excluded on the basis of $k_H/k_D = 2.2$; the transition state must be *late* in view of the high regioselectivity of the reaction and the observed Taft reaction constant.

A carbocationic process, in which the electrophilic peracid would first abstract a hydride, with the formation of $ArCOO^-$, H_2O, and R_3C^+ would not necessarily be at variance with the observed retention, although an extremely short lifetime of the cation would be required before conformational equilibration.[20] Such a mechanism has been found in the reaction of tri-*tert*-butylcyclopropene with *m*-chloroperbenzoic acid, which yields the particularly stable cyclopropenyl cation.[21] In view of the complete absence of ester, which should be expected for a trapping of the cation with $ArCOO^-$ anions, from the unreactivity of benzylic positions, and from the rather small ρ values, however, the cationic pathway seems to be less likely with normal alkanes. The abstraction of a poor leaving group such as a hydride in a nonpolar solvent would furthermore require higher activation enthalpies. Also, the large negative activation entropy is typical for a concerted oxenoid process but not for the formation of carbocationic intermediates, which only in charge-dispersing polar solvents are known to show such ΔS^* values.[22]

The hydroxylation described in this paper obviously represents the oxenoid process which was proposed by Hamilton[2b,11b] as one of the mechanistic possibilities for P-450 systems. Radical intermediates, which in our peracid reaction also lead to a remarkable loss of stereospecificity, have for the monooxygenases recently been favored on the basis of low stereoselectivity and large isotope effects.[2a,e] It should, however, be noted that high retention[23] and low isotope effects[2d] have been found in other cases and that the recent observation of ^{18}O incorporation into the enzyme effector lipoic acid would also

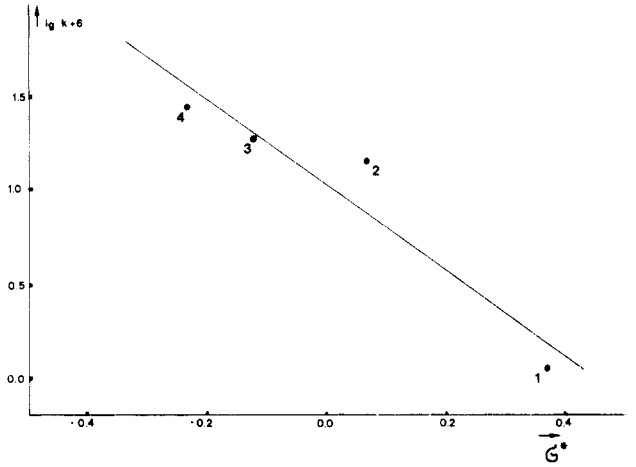


Figure 1. Taft plot for the reaction of *p*-nitroperbenzoic acid with substituted alkanes RMeCHR′: (1) R = Me, R′ = CH_2CH_2Cl; (2) R = Me, R′ = $CH_2CH_2CH_2Cl$; (3) R = Me, R′ = $CH_2CH_2CH_3$; (4) R = CH_3CH_2, R′ = $CH_2CH_2CH_2CH_3$. ($\rho^* = -2.2$, $r = 0.95$.)

Table III. Solvent Effects. Reaction of Methylcyclohexane with *p*-Nitroperbenzoic Acid[a]

solvent	I[a] k_{rel}	II[b] temp, °C	time, h	% conv
chloroform	1	60	5	25
chloroform–dioxane (5:1)	0.1	60	6	6
dioxane	0.02	65	6	3
chloroform–THF (5:1)	0.04	65	5	2
chloroform–EtOAc (15:1)[c]	0.6			
nitromethane		65	4	1

[a] From kinetic runs; rates k_{rel} were determined relative to chloroform ($k_{rel} = 1$). [b] From preparative experiments under similar conditions as described for **19** (see Experimental Section), practical conversions were determined in saturated solutions of the peracid. Due to the higher solubility of the acid in solvents other than chloroform the differences in % conversion are smaller than in k_{rel}. Solvent composition v/v; temperature, ±5 °C. [c] Only kinetic measurement with *tert*-butylcyclohexane (corrected for different absolute rate).

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(22) See, e.g.: Frost, A. A.; Pearson, R. G. "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961.

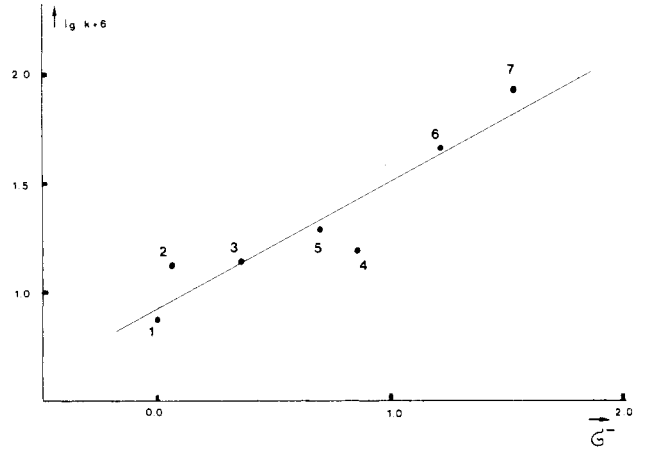

Figure 2. Hammett plot for the reaction of metylcyclohexane with substituted perbenzoic acids: (1) R = H; (2) R = *p*-F; (3) R = *m*-Cl; (4) R = *p*-CN; (5) R = *m*-NO_2; (6) R = *p*-NO_2; (7) R $_2$ = *m*,*m*-$(NO_2)_2$. (ρ = 0.57, r = 0.94.)

Table IV. Activation Parameters and Isotope Effect[a]

	$\Delta G^*_{298\,K}$, kcal mol^{-1}	ΔH^*, kcal mol^{-1}	ΔS^* cal K^{-1} mol^{-1}
1	25.39	18.8	−22
10	23.74	15.1	−29
16	25.84	17.2	−29
1-d_{14}	k_H/k_D = 2.2 ± 0.1 at 333 K		

[a] From measurements with *p*-nitroperbenzoic acid in chloroform.

agree with the formation of peracid derivatives, e.g., in bacterial camphor hydroxylase.[24] The involvement of peracid-related structures in monooxygenases[11a,b] seemed so far to be unlikely in view of the assumed low reactivity of peracids toward carbon–hydrogen bonds.[24] The present work, however, shows that with moderately activated peracids the alkane oxidation is to a large degree limited by entropic factors, which could be easily overcome in the active site of a protein.

Experimental Section

Kinetic Measurements. Solutions of 0.07 M peracid and 0.7 M hydrocarbon in distilled chloroform were thermostated; the exact peracid concentration was determined iodometrically before use. It was ascertained after completion that no more than 3% of the peracid was lost by decomposition. The hydrocarbon conversion was followed by GLC analysis of 1-mL samples after immediate mixing with 2 mL of 10% $NaHSO_3$ solution and drying over Na_2SO_4. The exact concentrations of peracid and substrate at elevated temperature were obtained with the expansion coefficient of chloroform. GLC analyses were calibrated with authentic samples of alkanes and their hydroxy derivatives. Least-squares evaluation of the concentration changes, usually from 0–1% conversion using the integrated rate equation for second-order kinetics gave linear plots (r > 0.99) and rate constants with an average standard derivation of ±2%. This method was used for rate determinations with the substrates **1**, **2**, **10**, **13**, and **16** (Table I). Activation parameters were obtained for **1**, **10**, and **16** (Table IV) by measurements at four to five temperatures in 10-degree intervals, yielding linear plots of ln (kT^{-1}) vs. T^{-1} (see supplementary material), ΔH^* with ±0.3 kcal mol^{-1}, and ΔS^* with ±1 cal K^{-1} mol^{-1} on the average. The kinetic isotope effect with perdeuteriomethylcyclohexane was determined by comparison to methylcyclohexane conversion at 60 °C after a 20-min reaction (Table IV).

Competition Kinetics. The rates of the other hydrocarbons (without hetero substituents) were determined by GLC analysis of relative velocities, using a substrate B with known rate constant k_2 and the second substrate A, both in 0.4 M concentrations in chloroform at 60 °C and in peracid in such a concentration, that after 6 h total conversion of substrate did not exceed 20%. The rate constant k_1 for substrate A was obtained from k_1/k_2 = log (A/A_0)/log (B/B_0), where A_0 and B_0 refer to the initial concentrations, A and B to the concentrations reached after ~20% conversion. Substrates with hetero substituents usually showed some decomposition during GLC after hydroxylation; their relative rates were therefore obtained from ^{13}C NMR analyses instead of from GLC.

Peracids were prepared by modifying the literature[25] procedure as follows: 25 g (0.15 mol) *p*-nitrobenzoic acid was dissolved in 72 g (0.75 mol) of methanesulfonic acid, and 18 g (0.45 mol) of hydrogen peroxide (85% iodometrically) was added dropwise under chilling with ice. After being stirred for 3 h at 40 °C the mixture was chilled; ice and then water were added so that the temperature did not rise above 25 °C; the precipitate was filtered and washed with ice–water to neutral reaction of the water. The peracid (24.8 g = 82%) was dried over silica gel; the iodometrically determined peracid content was 91%. The other peracids were prepared similarly, e.g., 3,5-dinitroperbenzoic acid (53% yield, 68% peracid content) and perbenzoic acid (reaction temperature, 20 °C; time, 2 h; saturated $(NH_4)_2SO_4$ solution instead of ice–water and extraction of the peracid with chloroform; 75% peracid content). Other peracids as well as most hydrocarbons were commercially available.

Hydroxylations were carried out under conditions described in Tables I–III or on a larger scale as described below. Quantitative analyses of the regio- and stereoselectivity were performed by GLC, which showed base line separation, e.g., for all six isomers which are possible by attack on CH and CH_2 bonds in the stereoisomeric 1,4-dimethylcyclohexanes. Primary alcohols were not observed (<1%). **Diols** (e.g., from **5** and **18**) were analyzed by ^{13}C NMR prior to aqueous workup.

Product Identifications. The structures were assigned on the basis of their ^{13}C NMR shifts, which could be measured in the raw products without further purification; they agreed within ±0.1 ppm with the literature data for the compounds derived from **1** and **2**,[26] for alcohols from **3**–**8**,[27] and for products from **9** and **10**,[28] from **11** and **12**,[13a] from **13** and **14**,[29a] from **15**,[29b] and from **32** and **34**.[30] The ^{13}C NMR shifts of the tertiary hydroxylation products from **16**–**24** were calculated by using known substituent increments for the OH group;[26-31] they agreed with the observed values within the expected range[26-31] and will be discussed in another context.[32] Some structures were in addition supported by comparison of symmetry and number of carbon signals (such as products from **17** or the dihydroxylation products from **5** and **18**) and/or by ^1H NMR observations, which allow to distinguish secondary from tertiary alcohols. ^{13}C NMR shift calculations for steroids were based on published data;[31] **37** (R = H; Y = H; X = OH) was known from the literature.[33] The other steroidal products could be unambiguously assigned on the basis of the consistent OH substituent effects on the ^{13}C NMR shifts of the corresponding skeletons;[31] at least seven observable shifts can be used to locate the hydroxyl group in each steroid (Table V).

(−)-2,6-Dimethyl-6-hydroxyoctane. (−)-2,6-Dimethyloctane[34] (**19**, 17 g = 0.12 mol) was refluxed with 27.2 g (0.14 mol) of *p*-nitroperbenzoic acid and 0.8 g of iodine in 200 mL of $CHCl_3$ for 30 h. After chilling, the precipitated acid was filtered off and

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(34) (*R*)-(−)-Tetrahydrocitronellene (Fluka).

Table V. Hydroxylation Experiments with Substrates from Table I. Reaction Conditions, Yields, and Product Distributions[a,e]

compd	R	peracid, mol	time	*t*-ROH, %	*sec*-ROH, %	diols, %	R_s^t
1	4-NO_2	1	*b*	29	3	<3	95 ± 5
1	3-Cl	1	*b*	19	4.5	<3	40 ± 5
1	3,5-$(NO_2)_2$	1	*b*	24	1	<3	240 ± 10
3	4-NO_2	<4	*c*	53	2.3	<4	90 ± 5
4	4-NO_2	1	*d*	53	2.2	<3	96 ± 5
4	4-NO_2	2	*c*	75	2.5	<4	120 ± 5
5	4-NO_2	1	*d*	47	2	15	95 ± 5
7	4-NO_2	1	*d*	47	1.3	<3	140 ± 10
8	4-NO_2	1	*d*	52	1.5	<3	140 ± 10
24	4-NO_2	2	*c*	45[f]	*g*	<5	*g*
9	4-NO_2	1	*c*	87	4	<5	160 ± 20
10	4-NO_2	1	*c*	72	3	<5	190 ± 20
10	3-Cl	1	*c*	46	7	<5	50 ± 5
11	4-NO_2	1	*c*	20[h]	1[h]	*g*	140 ± 20
12	4-NO_2	1	*c*	43.5	1	<5	300 ± 20
13	4-NO_2	1	*c*	53	1	*g*	150 ± 10
14	4-NO_2	1	*c*	21	*g*[i]	*g*	14 ± 2
15	4-NO_2	1	*c*	60[j]	4	*g*	60 ± 5
16	4-NO_2	1	*c*	33	10	*g*	13 ± 2
17	4-NO_2	1	*c*	42	8.5	*g*	20 ± 3
18	4-NO_2	2.8	*c*	53	4.5[k]	9	23 ± 3
19	4-NO_2	1.4	*c*	28.5[l]	5	<5	23 ± 3

[a] Product analyses refer to crude reaction mixture prior to purification, if any. Reactions in $CHCl_3$ under reflux with different perbenzoic acids ($R_nC_6H_{(5-n)}CO_3H$), using 1 mol of substrate and 1 or 2 mol of peracid, as denoted. Substrate concentration: 1 ± 0.2 M. [b] Run until peracid was used up (ca. 20 h). [c] 40 ± 4 h. [d] 18 ± 3 h. [e] Tertiary and secondary alcohols analyzed by GLC; primary alcohols not observed (<1%). Control experiments with authentic alcohol mixtures secured that secondary and primary alcohols—which were not structurally assigned—were separated from the tertiary main products under the GLC conditions applied. Yields were determined by GLC comparison to the starting hydrocarbon ($\sum$ = 100%). Diols analyzed in the raw reaction mixture by ^{13}C NMR. Other byproducts: up to 15% nitrobenzene (unless noted otherwise) (see text). Regioselectivity ratio R_s^t obtained from r = (*t*-ROH)/(*sec*-ROH) after statistical correction, e.g., by multiplication of r with a factor of 10 for **1**. Stereochemistry of the dominating alcohol: see % Ret in Table I; configuration of the secondary alcohols not determined. Errors from GLC analysis errors. Structural assignments by ^{13}C NMR (see text). Epimeric ratios see Table I. [f] ^{13}C NMR analysis only ±5%; 50% nitrobenzene as byproduct. [g] Not analyzed. [h] Only relative ratios *t*-ROH/*sec*-ROH determined. [i] Largely radical reaction; 50% nitrobenzene formed. [j] Predominately (~98%) exo-OH, endo-CH_3. [k] Including 9% diol. [l] From product distribution, see Table I.

extracted with $CHCl_3$; the organic layers were neutralized and dried over Na_2SO_4, and $CHCl_3$ was distilled off. Chromatography over silica gel (1.5-m column) with CH_2Cl_2 at 10 °C yielded 0.9 g (5%) of **19a** and 2.3 g (13%) of optically active 2,6-dimethyl-6-hydroxyoctane (**19b**), $[\alpha]^{20}_D$ −0.909° (lit.[35] $[\alpha]^{20}_D$ −0.78° (neat)] besides mixtures of **19a** and **19b**. All attempts to analyze the enantiomers with optically active NMR reagents failed. GLC retention times of **19b** agreed with those of the authentic material.

Steroid Hydroxylations. Steroid (1 g, 3.1 mmol), 1.15 g (6.2 mmol) of *p*-nitroperbenzoic acid (90%), and 0.05 g of iodine were refluxed in 10 mL of chloroform until the KI paper test for peracid was negative (40–60 h). The acid precipitate collected after cooling was extracted with ether; the combined organic layers were neutralized and dried over Na_2SO_4, and the residue obtained after evaporation of the solvents was chromatographed on silica gel (1.5-m column) with chloroform. The products and yield obtained after purification were as follows: 9α-hydroxy-3β,17β-diacetoxyandrostane (**37**, R = OAc; X = H; Y = OH; 10%) from **36** (R = OAc); 5α,9α-dihydroxy-17β-acetoxyandrostane (**37**, R = H; X = Y = OH; 25%, with 4 mol of peracid for 1 mol of **36**, R = H). A mixture of 9α-hydroxy- and 5α-hydroxy-17β-acetoxyandrostane[28] was obtained from **36** (R = H) by reaction with only 2 mol of peracid.

Experiments with Pertrifluoroacetic Acid. Reactions with this peracid, obtained from trifluoroacetic (TFA) anhydride and hydrogen peroxide (85%), yielded with several cycloalkanes (**1**, **7**–**9**) largely secondary esters, with R_s^t < 10 even at <10% conversion and reaction in chloroform (~4 M peracid, ~2 M **1**). Buffering with NaH_2PO_4 and Na_2HPO_4, which was successfully used in epoxidation,[36] did not substantially improve the selectivity but led to smaller yields by decomposition of the peracid.

1-Hydroxyadamantane, however, which is stable under the reaction conditions, could be obtained in 58% yield from **13**: 22.5 g (0.11 mol) of TFA anhydride, 2.25 g (0.02 mol) of free TFA, 3.1 g of H_2O_2 (85%, 0.09 mol), and 22 mL of $CHCl_3$ were mixed under chilling with ice, and 5 g (0.04 mol) of **13** was added. After 2 h at 20 °C the mixture was added to 40 mL of 5 N NaOH and extracted with 2 × 75 mL of ether. The solvent was distilled off and the residue saponified with KOH/20% CH_3OH at 80 °C for 1 h. After the usual workup and recrystallization from ethanol one obtained 3.24 g of pure product (experiments by H. Kropf).

Oxidation of Aromatic Compounds. Usually a 0.8 M solution of the arene in chloroform was heated to reflux with a 100% molar excess of *p*-nitroperbenzoic acid for 3 h and worked up as above. The products were analyzed by GLC and NMR and separated in the case of mesitylene oxidation by preparative TLC.

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Registry No. **1**, 108-87-2; **2**, 3178-22-1; **3**, 2207-04-7; **4**, 624-29-3; **5**, 638-04-0; **6**, 2207-03-6; **7**, 6876-23-9; **8**, 2207-01-4; **9**, 493-02-7; **10**, 493-01-6; **11**, 3296-50-2; **12**, 4551-51-3; **13**, 281-23-2; **14**, 280-33-1; **15**, 765-90-2; **16**, 107-83-5; **17**, 96-14-0; **18**, 592-13-2; **19**, 98611-99-5; **19b**, 80558-38-9; **20**, 5685-47-2; **21**, 279-23-2; **22**, 872-78-6; **23a**, 71-43-2; **23b**, 98-82-8; **23c**, 135-98-8; **23d**, 1603-61-8; **24**, 91306-65-9; **25**, 1900-69-2; **26**, 62016-94-8; **27**, 107-84-6; **28** (R = H), 108-95-2; **28** (R = Me), 100-66-3; **29**, 104-93-8; **30**, 86-73-7; **31**, 87-85-4; **32**, 108-67-8; **34**, 91-20-3; **36** (R = H), 1236-49-3; **36** (R = OAc), 5424-40-8; **37** (R = X = H, Y = OH), 98612-02-3; **37** (R = Y = H, X = OH), 38676-90-3; **37** (R = H, X = Y = OH), 98612-01-2; **37** (R = OAc, X = H, Y = OH), 98612-00-1; **H1** (X = NMe), 98634-01-6; **H1b**, 98612-03-4; **H1c**, 98634-02-7; **H1d**, 98612-04-5; **H2** (X = Y = NH), 93367-94-3; **H2a**, 93367-95-4; **H2c**, 98612-05-6; **H2d**, 98612-06-7; **H2e**, 98612-07-8; 4-$NO_2C_6H_4CO_2H$, 62-23-7;

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3,5-$(NO_2)_2C_6H_3CO_2H$, 99-34-3; C_6H_5COOH, 65-85-0; $C_6H_5CO_2OH$, 93-59-4; 4-$FC_6H_4CO_2OH$, 1514-03-0; 3-$ClC_6H_4CO_2OH$, 937-14-4; 4-$CNC_6H_4CO_2OH$, 1711-43-9; 3-$NO_2C_6H_4CO_2OH$, 2453-41-0; 4-$NO_2C_6H_4CO_2OH$, 943-39-5; 3,5-$(NO_2)_2C_6H_3CO_2OH$, 66358-48-3; F_3CCO_2OH, 359-48-8; $ClCH_2COOMe$, 96-34-4; 3-$BrCH_2C_6H_4COOMe$, 1129-28-8; 1-hydroxyadamantane, 768-95-6; deuterium, 7782-39-0; 3-(bromomethyl)-4-nitrobenzoic acid methyl ester, 88071-90-3.

Supplementary Material Available: Experiments with macrocyclic hosts for hydrocarbon oxidation and tables of ^{13}C NMR shifts and kinetic parameters (12 pages). Ordering information is given on any current masthead page.

A Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres Using Novel, Chiral Aminoalkyl Epoxides and γ-(Aminoalkyl) γ-Lactones

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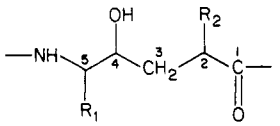
A stereocontrolled synthesis of the hydroxyethylene dipeptide isosteric unit 1 is described. This synthesis is capable of providing all eight stereoisomers of 1 and is amenable to variation of substituents R_1 and R_2. Also described are the novel chiral epoxides 2 and substituted γ-lactones 3, key intermediates in this synthesis having potentially broad application.

In the course of our work on peptidase inhibitors, we sought to prepare peptides containing suitable analogues in place of specific peptide bonds. Of particular interest were compounds incorporating the 2,5-disubstituted-5-amino-4-hydroxypentanoic acid unit, 1, the "hydroxyethylene dipeptide isostere", in this capacity. Only recently has interest in such subunits resulted in published syntheses,[1] and these have been of limited scope in terms of both variability of substituents and control of stereochemistry. The following method for synthesis of 1 allows wide and independent variation of the 2- and 5-substituents, as well as independent and controlled variation of stereochemistry at each of the stereocenters (2, 4, and 5) in 1.



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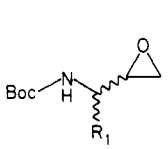
Results and Discussion

tert-Butylcarbonyl-(Boc) protected chiral α-amino aldehydes have served us well as useful intermediates in the preparation of statine ((3*S*,4*S*)-4-amino-3-hydroxy-5-methylhexanoic acid, Sta) and its analogues.[2] In extending our studies to include the statine homologues, 5-amino-4-hydroxy acids 1, we turned to these same aldehydes as potential intermediates. In preparing statine,[2] we had followed the example of Rich,[3] who had found that Boc-α-amino aldehydes could be synthesized and added to the enolate anion of ethyl acetate without significant loss of chirality, provided certain conditions of time (brief) and temperature (low) were observed.

Extending this observation, we surmised that the epoxides 2, synthetic intermediates of potentially broad utility, might also be prepared with retention of chirality by similarly careful addition of Boc-α-amino aldehydes to a suitably reactive ylide (Scheme I). To test this hypothesis most effectively, we chose as a pilot substrate the most chirally labile of the Boc-α-amino aldehydes we had so far encountered,[4] the compound **4a**, derived from Boc-L-Phe. It was with some surprise that we found dimethylsulfonium methylide[5] reacted with **4a** to give the desired epoxide **2**, not only in respectable yield but with virtually complete retention of chirality (see below).



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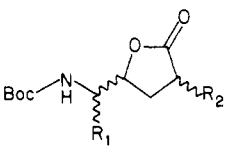

3

Ylide attack on the diastereotopic faces of the aldehyde proved largely nonspecific, so that the product obtained was in fact a separable mixture of two diastereomers, easily distinguished by the NMR absorption of the C_2 proton (δ 3.7 and 4.1). To distinguish the "erythro" (2*S*,3*S* = **2a** and/or 2*R*,3*R* = **2d**) from the "threo" (2*R*,3*S* = **2b** and/or 2*S*,3*R* = **2c**) diastereomers, X-ray crystallographic analysis of one of these separated isomers (C_2H = δ 4.1) was carried out, showing the compound to have the "threo" configuration (Figure 1). Thus, the "erythro" and "threo" isomers could be separated and identified readily by the NMR absorption of their C_2 proton ("threo" = δ 4.1, "erythro" = δ 3.7).

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