Experimental Section

Enol Lactone 5. $HClO_4$ (7 mL 70%) was added to the solution of the keto aldehyde **4** (533 mg, 2.0 mmol) in THF (10 mL) and water (10 mL). The whole solution was stirred for 7 h at room temperature. The mixture was partitioned between CH_2Cl_2 (50 mL) and water (15 mL) and then extracted, washed with brine, and dried ($MgSO_4$). The evaporation in vacuo gave a colorless oil, which was further purified on column chromatography (silica gel, 8/1 = $CHCl_3/CH_3OH$) to afford enol lactone **5**: 260 mg (52%); ^1H NMR ($CDCl_3$, Me_4Si) δ 6.72 (br s, 1 H, enol H), 3.19 (m, 1 H, O_2CCH), 2.4 (s, 3 H, CH_3CO); IR ($CHCl_3$) 1705 (C=O), 1650 (C=O, enol lactone) cm^{-1}.

Allylic Hydroperoxide 7. A stream of pure oxygen was admitted through a gas dispersion tube to a solution of (9*R*)-methyl artemisinate (**3b**; 500 mg, 2.0 mmol) and methylene blue (50 mg, 0.13 mmol) in anhydrous CH_3OH (30 mL). The mixture was irradiated by high mercury arc lamp during 2.5 h at room temperature. Evaporation in vacuo and purification by column chromatography (silica gel, 1/2 = EtOAc/hexane) afforded the allylic hydroperoxide **7** [401 mg (70%)] as a slightly yellow oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 5.27 (s, 1 H, CH=), 3.80 (s, 3 H, CO_2CH_3), 2.81 (m, 1 H, $CHCO_2$), 1.22 (s, 3 H, CH_3 at C-3); IR (neat) 3400 (OOH), 2940, 2560, 1740 (C=O), 1650, 1440, 1200, 1170, 760 (C=C) cm^{-1}.

Desoxyartemisinin (11). To the solution of the allylic hydroperoxide **7** (400 mg, 1.42 mmol) in dry $CHCl_3$ (6 mL) was added *m*-CPBA (360 mg, 2.08 mmol). The mixture was stirred at 0 °C for 1 h. Evaporation in vacuo and purification on column chromatography (silica gel, 1/2 = EtOAc/hexane) gave a solid. Recrystallization from cyclohexane afforded desoxyartemisinin (**11**) [240 mg (64%)] as a colorless crystal: mp 108–111 °C (cyclohexane) (lit.[7] mp 110–111 °C); $[\alpha]^{25}_D$ –99.75° (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 5.70 (s, 1 H, C-1), 3.21 (m, 1 H, C-9), 1.53 (s, 3 H, C-3); IR ($CHCl_3$) 1740 cm^{-1} (δ-lactone C=O); MS (70ev) *m/e* 266 (M^+). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.67; H, 8.27; O, 24.06. Found; C, 67.77; H, 8.33; O, 23.78.

Acknowledgment. This research was supported by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi. We express our thanks to Drs. Farouk El-Feraly, Mahmoud A. ElSohly, and Robert Sindelar for helpful discussions and Mr. Tim West for technical assistance.

Registry No. 1, 80286-58-4; 1 (methyl ester), 82869-24-7; **3b**, 87391-99-9; **4**, 105250-95-1; **5**, 105231-07-0; **7**, 85031-63-6; **11**, 72826-63-2.

Supplementary Material Available: Tables of crystal data, atomic positional and thermal parameters, bond lengths and angles, and torsion angles for desoxyartemisinin (**11**) (6 pages). Ordering information is given on any current masthead page.

A Proposed Kinetic Method for Improving the Optical Purity of Synthetic Peptides

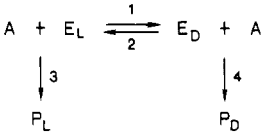
Eugene M. Holleran* and Joseph Kovacs

Chemistry Department, St. John's University, Jamaica, New York 11439

Received April 10, 1986

An important consideration in the synthesis of peptides is the optical purity of the product. Generally, the coupling of smaller peptides or amino acids, themselves optically pure to begin with, produces a product that is not optically pure. This is because the free amine group on one reactant catalyzes the racemization of the other reactant during the coupling. Thus some of the product is in the "wrong" isomeric form. This is a highly undesirable result, and much research has been devoted to minimizing its extent.[1-3] In this paper we explore the improvement of optical purity that might be gained by the simple means of using an excess concentration of the reagent that racemizes.

Scheme I



We represent the overall coupling reaction as A + E → P, where P is the peptide product. E can be an active ester, and A has a free amine group. The ester is originally all in the L form, E_L, but during the reaction it is partially converted to the D form, E_D, before coupling. Thus some of the product is the undesired diastereomer, P_D.

We assume the reaction in Scheme I as our working hypothesis. The isomeric forms of P are assumed to be stable and not to interconvert. This scheme differs from both the independent and the dependent parallel reaction schemes discussed in an overall treatment by Ugi, et al.[4]

We now inquire into the effect of three parameters, *r*, *x*, and *m*, on the purity of the product according to this scheme. The first, *r*, is the ratio A_0/E_0 of the initial concentrations of amine and ester. The second, *x*, is the fraction of E_0 that has reacted by any time, *t*. (Note that only if $r = 1$ will *x* also equal the fraction of A_0 reacted.) From these definitions we can express the concentrations of product and reactants as shown in eq 1. (Here, and

$$E = E_0(1 - x)$$
$$A = E_0(r - x) \qquad (1)$$
$$P = E_0x$$

subsequently, capital letters may be taken to represent concentrations.) At any time, $E = E_D + E_L$, and $P = P_D + P_L$. If the amine is in excess, then $r > 1$, and upon completion of the reaction, $x = 1$, $E = 0$, $A = E_0(r - 1)$, and $P = E_0$. On the other hand, if the ester is in excess, then $r < 1$, and at completion, $x = r$, $E = E_0(1 - r)$, $A = 0$, and $P = rE_0 = A_0$. In this case, the final, maximum value of *x* is less than one.

The third parameter, *m*, is defined as the ratio, k_r/k_c, of the racemization rate constant ($k_r = 2k_1 = 2k_2$) to the coupling rate constant ($k_c = k_3 = k_4$). (We are assuming for simplicity that the two optical isomers of *E* do not differ in their racemization rates or in their coupling rates.) In general, it is obvious that a small value of *m* favors product purity.

We define the extent of the product's optical impurity, *F*, as the fraction of the product in the D form, or $F = P_D/P$. We now determine exactly how this product impurity, *F*, depends on the rate constant ratio, *m*, the initial concentration ratio, *r*, and the extent of the reaction as defined by *x*. To do this we must first investigate the variation of E_D during the reaction, because it is from the D form of *E* that the D form of *P* is produced in step 4.

The rates, *R*, of the four steps in the reaction scheme can be expressed as shown in eq 2. Later, when we use ratios of these rates, the factor k_cA will always cancel out.

(1) Kemp, D. S. *The Peptides*; Gross, E., Meienhofer, J., Eds.; Academic: New York, 1979; Vol. 1, p 317.
(2) Kovacs, J., in ref 1, 1980; Vol. 2, p 529.
(3) Benoiton, N. L., in ref 1, 1983; Vol. 5, p 218.
(4) Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977**, *33*, 1353.

0022-3263/86/1951-5419$01.50/0

$$R_1 = k_1AE_L = (m/2)k_cAE_L$$
$$R_2 = k_2AE_D = (m/2)k_cAE_D$$
$$R_3 = k_3AE_L = k_cAE_L \quad (2)$$
$$R_4 = k_4AE_D = k_cAE_D$$

The rate of change of E_D can be expressed as $dE_D/dt = R_1 - R_2 - R_4$. This cannot be set equal to zero, as had been done,[5] because E_D is not in a steady state; it is not an "unstable" intermediate and is no more reactive than E_L. However, noting that $R_2 = (m/2)R_4$, we can write eq 3. For the overall coupling rate we have eq 4. Noting that

$$dE_D/dt = R_1 + R_2 - (m + 1)R_4 \quad (3)$$

$$dP/dt = E_0dx/dt = R_3 + R_4 \quad (4)$$

$E_L + E_D = E = E_0(1 - x)$, and from eq 2 that $(R_1 + R_2) = (m/2)(R_3 + R_4)$, we divide eq 3 by eq 4 and obtain eq 5. This differential equation, in the two variables, E_D and

$$dE_D/dx = mE_0/2 - (m + 1)E_D/(1 - x) \quad (5)$$

x, can be solved to give eq 6, a result that can be verified by differentiation to yield eq 5. From eq 6 we find the fraction of unreacted ester in the D form to be eq 7.

$$E_D/E_0 = \tfrac{1}{2}(1 - x)(1 - (1 - x)^m) \quad (6)$$

$$E_D/E = \tfrac{1}{2}(1 - (1 - x)^m) \quad (7)$$

Figure 1 illustrates this variation of E_D/E with x for several values of the rate constant ratio, m. Because only a small fraction of E is in the D form early in the reaction, the product being formed at small x is relatively pure. But eq 7 shows that as x goes to 1, which it does at completion if the ester is not in excess, E_D/E approaches $^1/_2$ for any finite m. This means that the last infinitesimal bit of ester to react and the last little bit of product to be formed are 100% "racemized". For relatively slowly racemizing esters this extreme is approached only when the reaction is very close to completion, but still it is obvious that in general, the last stages of reaction produce the most impure product, and it would be advantageous to avoid letting x approach 1. This can be done neatly and simply by using an excess of the ester so that the reaction automatically stops when $x = r$, which is less than 1. In practical coupling reactions m is very small, and Figure 1 shows that for small m a considerable reduction in racemization can be expected from stopping the reaction short of completion.

We now proceed to find the extent of product impurity at any x. We can find P_D from $dP_D/dt = R_4$ and from E_0 $dx/dt = R_3 + R_4$ (eq 8), so that the accumulated concentration of undesired product isomer at any x is shown in eq 9. The result of this integration, divided by $P = E_0x$,

$$(1/E_0)\, dP_D/dx = R_4/(R_3 + R_4) = E_D/E \quad (8)$$

$$P_D = (E_0/2)\int_0^x (1 - (1 - x)^m)\, dx \quad (9)$$

gives the fraction of product in the D form as shown in eq 10. We cited this result without derivation in our ref 6. Figure 2 shows how F depends on x for a small value of m.

$$F = P_D/P = \{mx + (1 - x)((1 - x)^m - 1)\}/2(m + 1)x \quad (10)$$

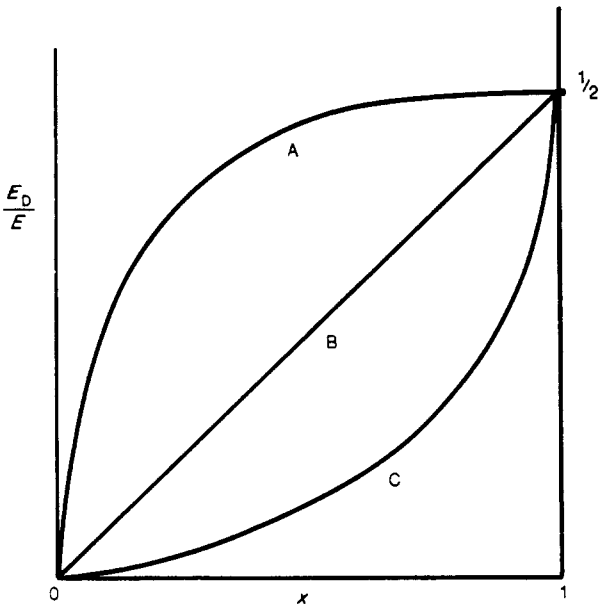


Figure 1. The fraction, E_D/E, of the unreacted ester, E, in the D form, E_D, as the reaction proceeds. (x is the fraction of E_0 that has reacted.) Curve A is for $m = 5$, B is for $m = 1$, and C is for $m = 0.2$.

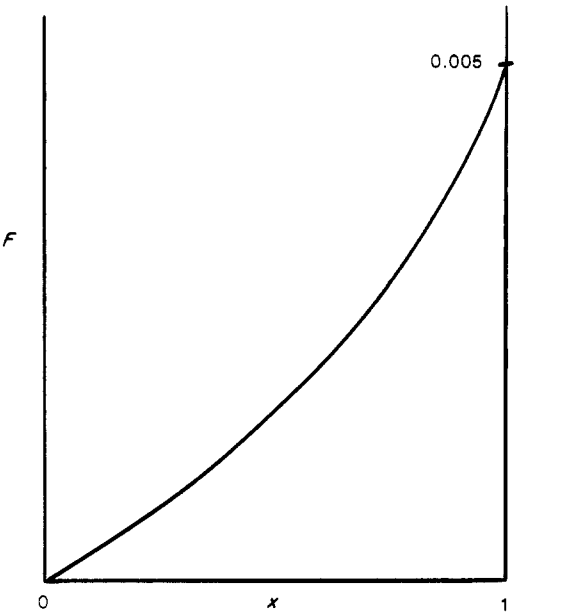


Figure 2. The fraction, $F = P_D/P$, of the product, P, in the form, P_D, for $m = 0.010$. For very small m, F approaches $m/2$ as x approaches 1.

From eq 10 we can draw the following conclusions. First we consider the case where E is not in excess, that is, where $r \geq 1$. In this case, x always equals 1 when the reaction is completed, and at this point the fractional impurity of the product is $F = (m/2)/(m + 1)$. For relatively fast racemization (large m), F approaches $^1/_2$, and for the most practical case of relatively slow racemization (small m), F becomes $m/2$. These correct results were previously derived invalidly from the steady-state assumption,[5] which gives $E_D/E = P_D/P = (m/2)/(m + 1)$ as constant throughout the reaction, i.e., independent of x, which it is not. In contrast, Figure 1 for E_D/E and Figure 2 for P_D/P show the important dependence of these quantities on the value of x, the fraction of E_0 that has reacted. It is precisely this dependence of F on x that is the basis of our proposed method of improving the optical purity of the coupled product by using an excess of ester, which

(5) Kovacs, J.; Mayers, G. L.; Johnson, R. H.; Cover, R. E.; Ghatak, U. R. *J. Org. Chem.* **1970**, *35*, 1810.
(6) Kovacs, J.; Jham, G. N.; Kim, S. E.; Hui, K. Y.; Holleran, E. M. *Peptides, Proceedings of the Sixth American Peptide Symposium*; Gross, E., Meienhofer, J., Eds.; Wiley: New York, 1979.

Table I. Percentage of Undesired Isomer in the Final Product ($100P_D/P$) for Various Values of $m = k_r/k_c$ and $r = E_o/A_o$, Assuming Complete Reaction of the Limiting Reactant, A

values of $r = E_o/A_o$	values of $m = k_r/k_c$				
	1	0.5	0.1	0.05	0.01
1	25.0	16.7	4.5	2.38	0.495
2	12.5	6.9	1.5	0.76	0.153
4	6.3	3.3	0.68	0.34	0.068
6	4.2	2.2	0.44	0.22	0.044
10	2.5	1.3	0.26	0.13	0.026

automatically limits the maximum value of x.

In this case of excess E, that is, for $r < 1$, x equals r when the reaction is completed. Since x never reaches 1, the impurity fraction does not reach $(m/2)/(m + 1)$. Table I shows the advantage in product purity to be gained by using various ratios of E_0 to A_0 for several selected small values of $m = k_r/k_c$, assuming the reaction goes until the limiting reagent, A, is depleted.

It is interesting to note that eq 10 does not show any explicit dependence of purity on the initial concentration ratio, r. But when r is less than one (excess E), it affects the product purity by limiting the maximum value of x to r. An excess of ester has the effect of terminating the reaction before the worst stage. An excess of the amine reactant has no effect at all on the product purity. This is because it has no effect on the extent of reaction of E at completion (100%); that is, the maximum value of x remains at 1 for all values of r greater than 1.

In actual practice, the reaction does not go all the way to completion because that would require, theoretically, an infinite time. But, as we have shown previously,[7] the time required for reaction of, say, 99% of the limiting reagent (A in our case) is considerably reduced by using an excess of the other reagent (E). From the usual second-order kinetics equations, the time required to reach a given x is, for $r = 1$, $t = x/(kA_0(1 - x))$, and, for $r < 1$, $t = (r \ln ((1 - rx)/(1 - x)))/(kA_0(1 - r))$. Applied to our case, these expressions show that the time required to react 99% of A is about *25 times* shorter when $E_0 = 2A_0$ ($r = {}^1/_2$), than when $E_0 = A_0$, ($r = 1$). An excess of E thus has the double effect of considerably shortening the reaction time and significantly improving the optical purity of the product. It is hoped that this strategem will prove useful in practical peptide synthesis.

(7) Kovacs, J.; Holleran, E. M.; Hui, K. Y. *J. Org. Chem.* **1980**, *45*, 1060.

Stereochemical Effects in Free Radical Hydrogen Abstraction from 2,3-Dichlorobutane

Nigel J. Bunce,* Henry K. Y. Cheung, and Jo-Anne Langshaw

Department of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, Canada, N1G 2W1

Received January 22, 1986

The stereochemical features of free radical hydrogen abstraction from a saturated carbon are almost unexplored. One relevant study is that of Dneprovskii et al.[1] who found that hydrogen abstraction from norbornane by a series of

(1) Dneprovskii, A. S.; Pertsikov, B. Z.; Temnikova, T. I. *J. Org. Chem. USSR (Engl. Transl.)* **1982**, *18*, 1951.

Table I. Chlorination of 2,3-Dichlorobutane Isomers

	isomer ratio[a] $1,2,3\text{-}Cl_3/2,2,3\text{-}Cl_3$	rel reactivity[b] $k(meso)/k(dl)$
Cl_2	*meso* 0.43 ± 0.01 (6)[c] *dl* 1.10 ± 0.04 (6)	1.10 ± 0.05 (6)
t-BuOCl	*meso* 0.16 ± 0.01 (3) *dl* 1.06 ± 0.02 (3)	0.64 ± 0.02 (3)

Relative Rate Constants

	k_1 (*meso*)	k_2 (*meso*)	k_1 (*dl*)	k_2 (*dl*)
$Cl^\bullet$	1.0[d]	7.0	1.6	4.3
t-$BuO^\bullet$	1.0[d]	18.8	5.8	16.5

[a] Isomer ratio = $3k_1/k_2$. Subscripts 1 and 2 refer to the numbering of the carbon chain in 2,3-dichlorobutane. [b] $k(meso)/k(dl) = [3k_1(meso) + k_2(meso)]/[3k_1(dl) + k_2(dl)]$. [c] Numbers in parentheses are the numbers of of independent experiments, each analyzed in triplicate. [d] Assumed.

radicals $ArICl^\bullet$ had values $k(exo)/k(endo)$ in the range 1.8-3.8. Abstraction by $Cl^\bullet$ from the same substrate was almost unselective, $k(exo)/k(endo) = 1.1 \pm 0.3$. Our interest in this stereochemical problem was sparked by the report of Lukas et al.,[2] who found that when a mixture of 2,4-dichloropentane isomers was photochlorinated, the *dl* isomer reacted slightly faster than the *meso*. Quantitative treatment[3] of the original data gave $k(dl)/k(meso) = 1.03$ for the overall hydrogen abstraction by $Cl^\bullet$ from these molecules. In this paper we examine the effect of neighboring chiral centres in the chlorination of 2,3-dichlorobutane by elemental chlorine and by *tert*-butyl hypochlorite. This substrate is easier to study than 2,4-dichloropentane because each dichlorobutane isomer has only two products of further monochlorination.

Experimental Section

All chlorinations were done in CCl_4 solvent at substrate concentrations <0.5 M using photoinitiation at room temperature (ca. 22 °C). Samples (2.0 mL) were sealed in vacuo into 8 mm o.d. Pyrex ampules by using the freeze-pump-thaw technique. In the experiments done in the presence of $CaCO_3$, the end of the ampule was blown out to give a round bulb, so that a micro magnetic stirring bar could be used to stir the mixture. All reaction mixtures were made up by mixing appropriate volumes of stock solutions of the reactants. For experiments where products were to be analyzed the ratio of substrate to chlorinating agent was always >10. Reaction mixtures were analyzed by VPC using gas chromatographs equipped with FID and electronic integration (Carle model 211 GC and Hewlett-Packard Model 3390 integrator or Carle Model 9500 GC and Spectraphysics "Minigrator"). VPC columns were 10% SE 30 on 60/80 mesh acid-washed Chromosorb W. Experiments were done at least in duplicate and were normally analyzed in triplicate. The response of the FID was assumed to be equal toward isomers.

tert-Butyl hypochlorite[4] and the separate isomers of 2,3-dichlorobutane[5] were obtained by the literature methods. Their purities by VPC were *dl* 96% and *meso* 97%. The mixed 2,3-dichlorobutane isomers were obtained commercially (Aldrich). The trichlorobutanes were obtained by chlorination, isolated by preparative VPC (elution order 2,2,3-trichlorobutane and then 1,2,3-trichlorobutane; the erythro and threo isomers of 1,2,3-trichlorobutane were not separable under our conditions), and analyzed by proton NMR at 400 MHz, using $CDCl_3$ as the solvent.[6]

(2) Lukas, R.; Palecková, V; Kolinský, M; Bârta, M. *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 3285.

(3) The original paper[2] gives percent of each isomer remaining at various stages of chlorination. Equation 1 allows a quantitative treatment. In eq 1, A and B are the substrates to be reacted competitively,

$$k_A/k_B = \ln ([A_o]/[A])/\ln ([B_o]/[B]) \quad (1)$$

$[A_o]$ and $[B_o]$ are the starting concentrations, and [A] and [B] are the concentrations after reaction.

(4) Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9.

(5) Lucas, H. J.; Gould, C. W. *J. Am. Chem. Soc.* **1941**, *63*, 2541.

0022-3263/86/1951-5421$01.50/0