complement to previously reported methods. Bichalcones serve as important synthetic intermediates in the syntheses of various biflavonoids differing in the oxidation level of the C_3 unit. Our procedure should therefore be applicable to nearly all natural biflavonoids through the intermediacy of bichalcones prepared from suitably substituted chalcones. Moreover, our results indicate that iodine in alkaline methanol is a simple and very useful reagent for phenol oxidative coupling. Its synthetic utility could well be exploited in those instances where the phenolic groups are hydrogen bonded. The hydrogen-bonded hydroxyls have been reported[7] to resist oxidation.

Experimental Section

Melting points were determined on a Kofler microscopical hot stage and are uncorrected. IR and UV spectra were obtained on Pye Unicam SP3-100 and PU 8800 spectrophotometers, respectively. NMR spectra were measured with a Varian A-60D instrument, and mass spectra with a JEOL JMS-D300 instrument.

Preparation of 2′-Hydroxy-4,4′,6′-trimethoxychalcone (1). To a mixture of phloroacetophenone-4,6-dimethyl ether (5 g, 25.5 mmol) and *p*-anisaldehyde (3.47 g, 25.5 mmol) in alcohol was added a hot 50% aqueous solution of sodium hydroxide (10 g). The resulting mixture was heated at 50 °C for 30 min. The contents were then cooled and poured into cold water and neutralized with dilute HCl. A yellow solid was obtained that was filtered, washed, and dried. Crystallization from alcohol yielded yellow needles of **1** (5.85 g, 73%), mp 112–114 °C (lit.[14] mp 113–114 °C).

Preparation of 2′-Hydroxy-4,4′-dimethoxychalcone (3). To a cold suspension of equimolar amounts of 2-hydroxy-4-methoxyacetophenone (8 g, 50 mmol) and *p*-anisaldehyde (7 g, 50 mmol) in alcohol (160 mL) was added a cold 60% aqueous solution of potassium hydroxide (95 g). The flask was stoppered securely and allowed to stand at room temperature for 1 week with occasional shaking. The contents were then poured on to crushed ice and neutralized with dilute HCl to give a yellow precipitate. The crude solid was filtered, washed with water, dried, and crystallized from methanol to afford yellow needles of **3** (10.4 g, 74%), mp 89–91 °C (lit.[7] mp 90–91 °C).

2′,2‴-Dihydroxy-4,4′,4″,4‴,6′,6‴-hexamethoxy[5′,5‴]bichalcone (2). 2′-Hydroxy-4,4′,6′-trimethoxychalcone (314 mg, 1 mmol) was dissolved in methanol, and a methanolic solution of potassium hydroxide (0.5 g) was added to it. To the resulting mixture was added iodine (127 mg, 0.5 mmol) with shaking. The contents were stirred at room temperature for 3 h and poured into ice-cold water. A red solid precipitated that was filtered, washed with water, and dried. Crystallization from alcohol yielded red crystals of **2** (220 mg, 70%), mp 189–191 °C (lit.[13] mp 191–192 °C): UV λ_{max} (MeOH) 228, 350, 370 nm; IR ν_{max} (KBr) 3440, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 3.80–4.00 (18 H, s, 4,4′,4″,4‴,6′,6‴-OCH_3), 5.62 (2 H, s, 3′,3‴-H), 6.90 (4 H, d, J = 9 Hz, 3,5,3″,5″-H), 7.50 (4 H, d, J = 9 Hz, 2,6,2″,6″-H), 7.65 (4 H, s, $\alpha,\beta,\alpha',\beta'$-H), 14.35 (2 H, s, 2′,2‴-OH); MS, m/z (relative intensity) 626 (M, 80.68), 611 (8.62), 519 (3.56), 493 (6.54), 492 (13.56), 491 (10.10), 465 (15.48), 464 (22.49), 463 (56.86), 461 (20.19), 358 (16.42), 357 (3.14), 327 (21.43), 314 (20.24), 313 (8.92), 312 (11.73), 301 (11.64), 194 (16.37), 179 (12.16), 180 (4.50), 161 (19.41), 134 (60.21), 133 (22.85), 121 (100).

Oxidation of 2. A mixture of **2** (100 mg) and SeO_2 (0.5 g) in isoamyl alcohol was refluxed for 24 h. The contents were then poured on the crushed ice. A solid precipitated that was filtered, washed with water, and dried. Crystallization from a chloroform/methanol mixture gave succedaneaflavone hexamethyl ether. Melting point, TLC, and NMR spectrum were in good agreement with that reported in the literature.[13]

2′,2‴-Dihydroxy-4,4′,4″,4‴-tetramethoxy[3′,5‴]bichalcone (4). The reaction was performed in the previously described manner. Thus, 2′-hydroxy-4,4′-dimethoxychalcone (500 mg, 1.76 mmol) was dissolved in methanol and a methanolic solution of potassium hydroxide (1 g) was added to it with shaking. Iodine (112 mg, 0.88 mmol) was added to the resulting mixture and the contents were stirred at room temperature for 3 h and poured into ice-cold water. The organic material was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow solid, which was crystallized from alcohol to give crystals of **4** (370 mg, 74%), mp 180–181 °C; UV λ_{max} (MeOH) 210, 230, 330, 380 nm; IR ν_{max} (KBr) 3440, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.85, 3.90, 4.00, 4.03 (3 H, each, s, 4,4′,4″,4‴-OCH_3), 6.65 (1 H, s, 3‴-H), 6.90 (7 H, mc, 5′,α,α',3,5,3″,5″-H), 7.75 (7 H, mc, 6′,β,β',2,6,2″,6″-H), 8.30 (1 H, s, 6‴-H), 13.60 (1 H, s, 2′-OH), 14.00 (1 H, s, 2‴-OH); MS, m/z (relative intensity) 567 (3.21), 566 (M, 19.23), 565 (30.64), 459 (4.62), 458 (3.29), 433 (14.19), 432 (19.61), 405 (45.23), 404 (67.32), 326 (16.73), 325 (28.11), 299 (18.31), 271 (8.67), 163 (7.35), 161 (67.32), 150 (1 4.59), 149 (10.95), 135 (24.45), 134 (100), 133 (34.56), 121 (28.91).

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Registry No. 1, 3420-72-2; 2, 57290-97-8; 3, 2198-19-8; 4, 105281-48-9; phloroacetophenone 4,6-dimethyl ether, 90-24-4; 2-hydroxy-4-methoxyacetophenone, 552-41-0; *p*-anisaldehyde, 123-11-5; succedaneflavone hexamethyl ether, 57290-98-9.

(14) Geissman, T. A.; Clinton, R. O. *J. Org. Chem.* **1946**, *81*, 697.

Practical Conversion of Artemisinic Acid into Desoxyartemisinin

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Artemisinin (Qinghaosu, **2**) isolated from *Artemisia annua* has recently been used in China as a new type of antimalarial drug with rapid action and low toxicity against chloroquine-resistant malaria.[3,4] Artemisinin is a novel sesquiterpene lactone bearing an unusual cyclic peroxide function. The combination of an interesting biological activity, a novel chemical structure, and a low yield from natural sources prompted us to search for a new synthesis of artemisinin and related compounds. Although interesting syntheses[5-7] of artemisinin and desoxyartemisinin were reported recently, these complex syntheses do not provide feasible methods for large-scale production. *A. annua* has been found to contain approximately 8–10 times more artemisinic acid than artemisinin.[8] We therefore attempted a new synthesis that embodies highly stereospecific conversion of artemisinic acid (**1**) into artemisinin (**2**) (Scheme I). Stereoselective reduction[7] of artemisinic acid (**1**) [$LiBH_4$ (5.3 equiv), $NiCl_2{\cdot}6H_2O$ (0.49 equiv), CH_3OH, room temperature, 2 h] into the dihydro compound **3a** (quantitative yield), followed by ozonolysis[7] of **3a** (O_3, CH_2Cl_2/CH_3OH = 1/1.5, −78 °C for 1 h and then CH_3SCH_3 workup), gave the keto aldehyde **4**, 75%.

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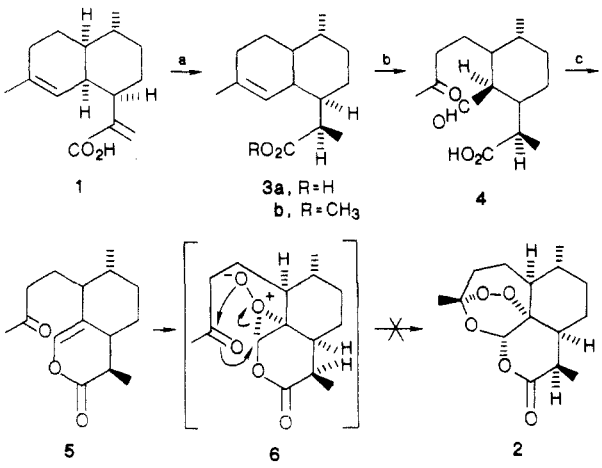
(3) Qinghaosu Antimalaria Coordinating Research Group Yaoxue *Tongbao* **1979**, *14*, 49.
(4) Qinghaosu Antimalaria Coordinating Research Group *Chin. Med. J.* **1979**, 92.
(5) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624.
(6) Xu, X.; Zhu, J.; Huang, D.; Zhou, W. *Acta Chim. Sin.* **1983**, *41*, 574.
(7) Xu, X.; Zhu, J.; Huang, D.; Zhou, W. *Tetrahedron* **1986**, *42*, 818.
(8) ElSohly, H. N.; Croom, E. M.; ElSohly, M. A.; Jung, M., unpublished result.

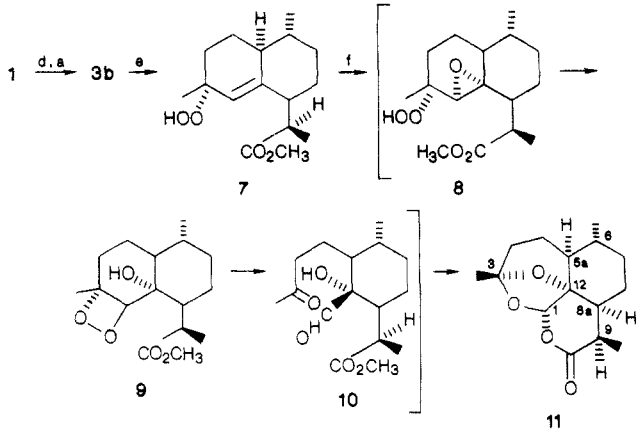
0022-3263/86/1951-5417$01.50/0

Scheme I[a]



[a] Key: (a) $LiBH_4$ (5.3 equiv), $NiCl_2 \cdot 2H_2O$ (0.49 equiv), CH_3OH, room temperature; (b) O_3, CH_2Cl_2/CH_3OH = 1/1.5, −78 °C, 1 h, then CH_3SCH_3 workup; (c) 70% $HClO_4$, THF/H_2O = 1/1, room temperature, 7 h.

Scheme II[a]



[a] Key: (a)–(c) see Scheme I; (d) CH_2N_2, Et_2O, room temperature, 20 min; (e) $^1O_2$, methylene blue, CH_3OH, room temperature, 2.5 h; (f) *m*-CPBA, $CHCl_3$, 0 °C, 1 h.

Compound **4** bearing a free acid group was successfully cyclized (70% $HClO_4$, THF/H_2O = 1/1, room temperature, 7 h) into the enol lactone **5**, 52%. For photooxidation[5,7] of **5** into artemisinin (**2**), all attempts of chiral addition of activated oxygen (high mercury arc lamp with methylene blue or hematoporphyrin as a sensitizer) via the transition state **6** have been unsuccessful. This might be due to decreased electron density of the double bond attached to the electron-withdrawing ester group within the enol lactone ring. During these synthetic studies on artemisinin, we found an interesting new conversion of artemisinic acid (**1**) into desoxyartemisinin (**11**)[6,13] in natural configuration (Scheme II). Thus, esterification[7] of artemisinic acid (**1**) (CH_2N_2, ethyl ether, room temperature, 20 min) (98%), followed by stereoselective reduction of α,β-unsaturated bond, afforded the dihydro artemisinic methyl ester **3b**, 95%. Stereoselective and regiospecific photooxidation[9,10] of **3b** ($^1O_2$, methylene blue, CH_3OH, room temperature, 2.5 h) provided the allylic hydroperoxide[11,12] **7** as a stable form: oil; 70%. Compound **7** is a versatile intermediate to obtain

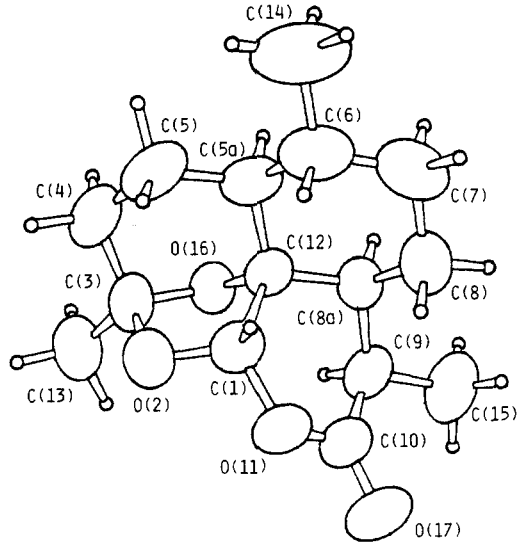


Figure 1. ORTEP plot of the structure of **11**, small circles denoting hydrogen atoms.

structural analogues of artemisinin. Thus, epoxidation (*m*-CPBA, $CHCl_3$, 0 °C, 1 h) of **7** gave a sesquiterpene lactone **11** in one step[7,13] (64%). We rationalize this result as follows: preliminary stereospecific α-face addition of oxygen into the double bond of **7** could give the epoxide **8**. Epoxide ring opening of **8** to give the 1,2-dioxetane **9** could be followed by cyclic peroxide ring cleavage of **9** to afford the keto aldehyde **10**. Finally, facile cyclization of **10** would result into desoxyartemisinin (**11**). The absolute configuration of **11** at C-1, C-3, C-5a, C-6, C-8a, C-9, and C-12 was established unequivocally by single-crystal X-ray analysis as 1*S*, 3*R*, 5a*S*, 6*R*, 8a*S*, 9*R*, and 12*R*; thus, three new chiral centers (C-1, C-3, and C-12) were generated in natural configuration. The crystal structure was solved by direct methods.[14] Full-matrix least-squares adjustment of non-hydrogen atom positional and thermal parameters, with hydrogen atoms included at their calculated positions, converged to R = 0.043 (R_w = 0.063).[15] A view of the solid-state conformation is provided in Figure 1. The 1,3-dioxalane ring is in an envelope form with O-16 as the out-of-plane atom.[16] Endocyclic torsion angles in the δ-lactone ring[16] are related by an approximate mirror plane of symmetry passing through C-8a and 0-11, and, with very small values for two adjacent angles, this ring has a half-boat (envelope) form.

Although desoxyartemisinin shows no antimalarial activity, this is an important metabolite for toxicology studies. This synthesis requires only four steps from readily available, optically active starting material **1** and proceeds in 42% overall yield. In conclusion, this process demonstrates a new and practical synthesis of desoxyartemisinin from artemisinic acid. Conversion of artemisinic acid and desoxyartemisinin into artemisinin is still under investigation.

(9) Marshall, J. A.; Hochstetler, A. R. *J. Org. Chem.* **1966**, *31*, 1020.
(10) Schultz, A. G.; Schlessinger, R. H. *Tetrahedron Lett.* **1970**, 2731.
(11) Xu, X.; Huang, D.; Zhu, J.; Zhou, W. *Acta Chim. Sin.* **1982**, *40*, 1081.
(12) Xu, X.; Zhu, J.; Zhou, W. *Acta Chim. Sin.* **1985**, *43*, 48.
(13) Hydrogenation of artemisinin in the presence of a $Pd/CaCO_3$ catalyst causes loss of one of the biologically important peroxide oxygens to give desoxyartemisinin. See:China Coorperative Research Group on Qinghaosu and Its Derivatives as Antimalarials *J. Trad. Chin. Med.* **1982**, 2(1), 9. Desoxyartemisinin isolated from *A. annua* is also the biotransformation product in the body. See: Zhu, D.; Huang, B.; Chen, Z.; Yin, M. *Yao Hsueh Hsueh Pao* **1980**, *15*(8), 509.
(14) Main, P. *MULTAN11/82*; University of York: York, England, 1982.
(15) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = |\sum(|F_o| - |F_c|^2)/\sum w|F_o|^2]^{1/2}$.
(16) Endocyclic torsion angles (ω_{ij}) about the bonds between atoms C-*i* and C-*j* follow (deg): $\omega_{1,2}$ 3.8; $\omega_{2,3}$ 22.6; $\omega_{3,16}$ −41.5; $\omega_{12,16}$ 42.5; $\omega_{1,12}$ −28.1 in the 1,3-dioxalane ring $\omega_{1,11}$ 0.5; $\omega_{1,12}$ −25.9; $\omega_{8a,12}$ 52.9; $\omega_{8a,9}$ −56.7; $\omega_{9,10}$ 34.5; $\omega_{10,11}$ −5.3 in the δ-lactone ring.

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.

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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

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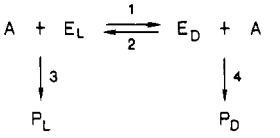
An important consideration in the synthesis of peptides is the optical purity of the product. Generally, the coupling of smaller peptides or amino acids, themselves optically pure to begin with, produces a product that is not optically pure. This is because the free amine group on one reactant catalyzes 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