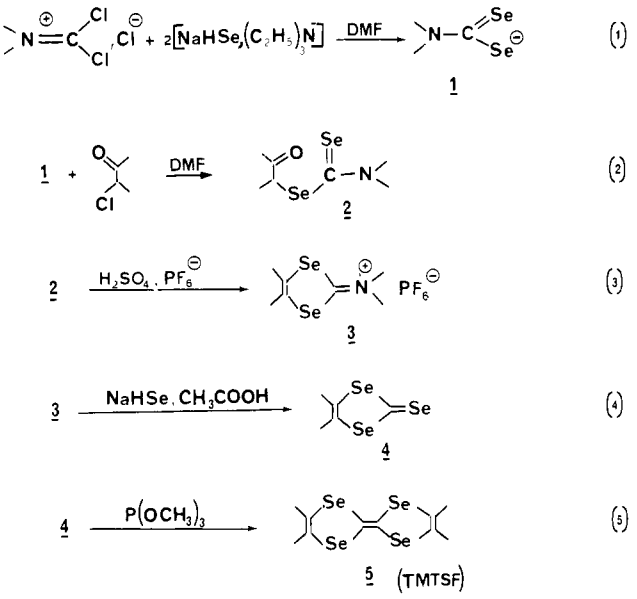
Scheme I



We have modified this latter procedure and use NaHSe in DMF–$(CH_3)_3COH$ to obtain comparable yields without handling gaseous H_2Se.

The reaction sequence is outlined in the Scheme I.

We generate NaHSe in DMF by reducing black selenium with a slight excess of $NaBH_4$. We use $(CH_3)_3COH$ as the proton donor needed to form NaHSe in an otherwise aprotic solvent.[18] $(CH_3)_3COH$ rather than primary or secondary alkohols is used to avoid side reactions of the reactive *N,N*-dimethylphosgeneimminium chloride.[19] Actually use of CH_3CH_2OH resulted in very low yields.

Also we found that NaHSe generated in C_2H_5OH[17] gave very high yields in step 3 (>92%) provided that the solution is "acidified" with 1 equiv of acetic acid.

Finally, we investigated the phosphite coupling[9,17] (step 5) which in our hands has not been very reproducible (yields ranging from 30 to 90%) and found that we reproducibly obtain yields better than 90% using Wudl's procedure[17] if the phosphite is redistilled *immediately* before use.

In conclusion, we report a modified synthesis of TMTSF from cheap and relatively nontoxic starting materials which gives a satisfactory overall yield.

Experimental Section

2-(Dimethylimino)-4,5-dimethyl-1,3-diselenolium Hexafluorophosphate (3). Powdered selenium (0.06 mol) in DMF (dried by passage through Al_2O_3, Woelm, basic, Super 1) containing 0.18 mol of $(CH_3)_3COH$ is stirred under argon,[20] and 0.06 mol $NaBH_4$ is added in small portions (~0.5 h). When the primary hydrogen evolution ceases, the stirred mixture is heated at 100 °C until colorless. Depending on the $NaBH_4$ quality, a small excess may be needed. The solution is cooled to 0 °C in ice, and 0.06 mol triethylamine is added. Solid *N,N*-dimethylphosgeneimminium chloride (0.03 mol, Fluka) is added slowly (20 min) from a side arm. The resulting solution is stirred at room temperature for 3 h and recooled in ice. 3-Chlorobutanone (0.03 mol, Fluka, redistilled) in 20 mL of DMF is added quickly. After 10 min, 50 mL water is added, the argon shield is removed, and the dark brown solution is stirred 30 min in air to oxidize eventual Se^{2-} or HSe^-. The solvents are removed on a rotary evaporator. The resulting (stinking) oil is treated with water, taken up in 200 mL of CH_2Cl_2, and washed twice with 100 mL of water. After the mixture is dried over $MgSO_4$ the solvent is removed on a rotary evaporator to yield 6–10 g of red oil, which is cyclized without further purification. The cyclization is obtained by dissolving the oil slowly (~20 min) in ice-cooled concentrated H_2SO_4. The H_2SO_4 solution is stirred for 2 h and poured into a mixture of 200 g of ice and 20 mL of 60% HPF_6 under vigorous stirring. The solid is recovered by filtration, washed with water, and dissolved in 50 mL of CH_2Cl_2 on the filter. After filtration, the solution is dried over $MgSO_4$ and filtered and the salt precipitated with ether to give, after drying, 5.5 g (44%) of **3** as a brown-yellow powder.[17] In some cases lower yields (26–35%) were obtained.

4,5-Dimethyl-1,3-diselenole-2-selone (4). Black, powdered selenium is reduced in absolute EtOH (30 mL/g of Se) with a slight excess of $NaBH_4$[18] under argon.[20] The colorless solution is cooled to −10 °C, and in quick succession 1 equiv of CH_3COOH and (solid) **3** are added. The solution is stirred under argon 2 h and allowed to warm to room temperature. The ethanol is diluted to 50% with ice–water, and the red solid is filtered, washed, with water and vacuum dried over P_2O_5. Recrystallization from toluene–heptane (1:1) gives pure **4**[10] in 92% yield after workup of the mother liquor.

Acknowledgment. This work was supported by ANVAR Grant No. 650-586.

Registry No. 1, 29891-77-8; 2, 76371-67-0; 3, 84041-23-6; 4, 53808-62-1; 5, 55259-49-9; Se, 7782-49-2; NaHSe, 12195-50-5; *N,N*-dimethylphosgeneimminium chloride, 33842-02-3; 3-chlorobutanone, 4091-39-8.

(15) Wudl, F.; Nalewajek, D. *J. Chem. Soc., Chem. Commun.* **1980**, 866.
(16) Chiang, L.; Poehler, T. O.; Bloch, A. N.; Cowan, D. O. *J. Chem. Soc., Chem. Commun.* **1980**, 866.
(17) Wudl, F.; Aharon-Shalom, E.; Bertz, S. H. *J. Org. Chem.* **1981**, *46*, 4612.
(18) Klayman, D. L.; Scott-Griffin, T. *J. Am. Chem. Soc.* **1973**, *95*, 177.
(19) Viehe, H. G.; Janouzek, Z. *Angew. Chem., Int. Ed. Engl.* **1973**, *2*, 806.
(20) Strict exclusion of O_2 is necessary during these procedures. A convenient trap for eventual H_2Se in the effluent argon is dilute NaOH (2 M) containing 2–5% H_2O_2, thereby producing elemental selenium.

Regioselective Hydroxylation of π-Allylpalladium Complexes with the $MoO_2(acac)_2$-*t*-BuOOH Catalyst System

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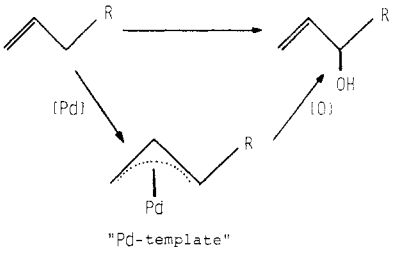
The "templated" reaction via π-allyl–metal intermediates formed from olefins has been of interest because they provide regio- and stereoselective introduction of various functional groups at allylic position of the parent olefins.[1] For the reaction of π-allylpalladium complexes with carbanions, the mechanism of regio- and stereocontrol and its application to organic synthesis have been extensively studied.[2] However, there has been little information about selective C–O bond formation via π-allylpalldium,[3,4] e.g.:

(1) (a) Baker, R. *Chem. Rev.* **1973**, *73*, 487. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (d) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer Verlag: West Berlin, 1980.
(2) For example, see: (a) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietshe, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3416, 3426. (b) Trost, B. M.; Verhoeven, T. R. *Ibid.* **1978**, *100*, 3435.
(3) (a) Vedejs, E.; Salomon, M. F.; Weeks, P. D. *J. Organomet. Chem.* **1972**, *40*, 221. (b) Jones, D. N.; Knox, S. D. *J. Chem. Soc., Chem. Commun.* **1975**, 166. (c) Muzart, J.; Pale, P.; Pete, J.-P. *Ibid.* **1981**, 668. (d) Hüttel, R.; Christ, H. *Chem. Ber.* **1964**, *97*, 1437.
(4) For the catalytic acetoxylation via π-allylpalladium, Bäckvall and Nordberg have reported that in the presence of chloride ligands mainly external trans attack of the acetate anion (AcO^-) on the π-allylpalladium complex takes place; in the absence of chloride ligands both cis and trans attack can occur depending on the AcO^- concentration. See: Bäckvall, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959.

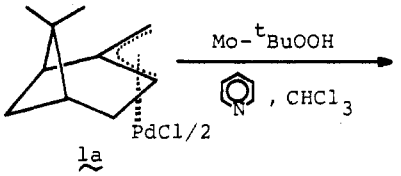
0022-3263/83/1948-0389$01.50/0

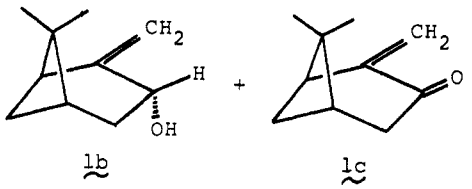
(a) oxidation of π-allylpalladium complexes with Collins reagent affords carbonyl compounds, the the regioselectivity of the products shows no regularity; (b) steroidal π-allylpalladium complexes are oxidized to allylic alcohols stereoselectively by MCPBA (*m*-chloroperbenzoic acid); (c) photolysis of π-allylpalladium complexes under an oxygen atmosphere leads to α,β-unsaturated carbonyl compounds without controlling the selectivity. Here we report the regioselective allylic oxidation of olefins via π-allylpalladium complexes catalyzed by a molybdenum and *tert*-butyl hydroperoxide system. The reaction is stoichiometric in *t*-BuOOH and catalytic in molybdenum. The regioselectivity for this allylic alcohol formation is opposite that for the C–C bond formation (eq 1).



(1)

By use of the $MoO_2(acac)_2$–*t*-BuOOH reagent, various π-allylpalladium complexes were oxidized in chloroform solution with excess of pyridine. These results are shown in Table I. The complexes **1a–5a** and **7a** were oxidized to allylic alcohols **1b–5b** and **7b**, and small amounts of the corresponding ketones were also formed. These alcohols are formed by hydroxylation at the internal allylic position of the original complexes. Neither primary allylic alcohols nor α,β-unsaturated aldehydes were detected. The complex **6a** derived from the internal olefin was also oxidized to 2-cyclohexenol (**6b**). Oxidation of pinene π-allylpalladium complex **1a** (eq 2) gave *trans*-pinocarveol (**1b**,



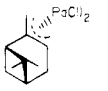
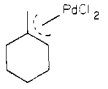
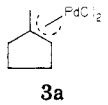
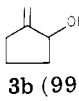
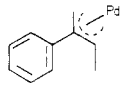
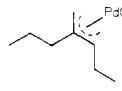
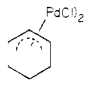
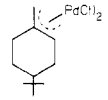


(2)

43% yield) and pinocarvone (**1c**, 9%), but the cis isomer was not detected. This result shows that oxygen attack at the π-allyl moiety occurs on the same face as that originally occupied by palladium. The identical stereochemistry can be observed in the oxidation of **7a**. The complex **7a** derived from 4-*tert*-butylmethylenecyclohexane consists of two stereoisomers, and the equilibrium between the complexes is fast under mild conditions.[2a] Considering the stereoelectronic background, oxygenation involves a strong preference for axial attack from the Pd side of the complex. So, *trans*-5-*tert*-butyl-2-methylenecyclohexanol (**7b**) was essentially obtained.

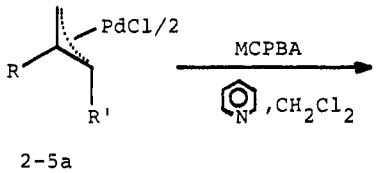
In the oxidation of steroidal π-allylpalladium complexes by MCPBA, Jones and Knox have reported similar stereochemistry concerning allylic alcohol formation.[3b] Hence, we carried out the oxidation of the complexes **1a–6a** using MCPBA. The complexes **1a** and **6a** were oxidized to give the corresponding allylic alcohols in 62% and 19% yields,

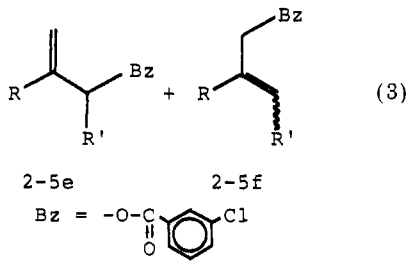
Table I. Oxidation of Various π-Allylpalladium Complexes Catalyzed by $MoO_2(acac)_2$-*t*-BuOOH[a]

complex	% conversion[b]	oxygenation products (selectivity,[c] %)
 1a	52	 1b (83)  1c (17)
 2a	57	 2b (99)
 3a	55	 3b (99)
 4a	50[d]	 4b (96)
 5a	58	5b (90)
 6a	63	 6b (49)  6c (15)  6d (13)
 7a	68	 7b (89)

[a] Reaction conditions: Pd complex/pyridine/$MoO_2(acac)_2$/*t*-BuOOH ratio of 1.0:5.0:0.1:1.2, $CDCl_3$ solvent, under N_2, 60 °C, 24 h. [b] Conversion was determined by the NMR spectrum of the remaining π-allyl complex; $CHBr_3$ was used as an internal standard. [c] Selectivity was determined by GLC. [d] Reaction time was 72 h.

respectively.[5] However, **2a–5a** produced two regioisomers of allylic benzoates without allylic alcohol formation[6] (eq 3). The ratios of the isomers were as follows: **2e** (attack





(3)

of MCPBA at the internal position)/**2f** (at the terminal position), 1:1; **3e/3f**, 3:2; **4e/4f**, 3:2; **5e/5f**, 2:3. From above results, MCPBA oxidation of π-allylpalladium complexes to give allylic benzoates was lacking in regioselectivity. In

(5) On addition of isopropyl alcohol, the yields of the allylic alcohols were fairly increased to 86% for **1b** and 29% for **6b**, respectively.

(6) Harvie, I. J.; McQuillin, F. J. *J. Chem. Soc., Chem. Commun.* **1976**, 369.

the case of MCBA (*m*-chlorobenzoic acid) instead of MCPBA with or without pyridine, the expected benzoates could not be obtained.

It should be noted that the regio- and stereoselectivities of this Mo-catalyzed hydroxylation are quite different from those of the C–C bond formation with carbanions.[4,7] In the case of C–C bond formation, Trost et al. reported that active methylene compounds generally attack at the less hindered side of the π-allyl moiety and that the alkylation occurs on the face of the π-allyl unit opposite that of the palladium.[2] On the contrary, in this C–O bond formation, an oxygen species attacks at the more hindered side of the parent olefin and on the same face of the π-allyl unit as that originally occupied by palladium.

A remarkable solvent effect was observed in this oxidation. Chlorohydrocarbon solvents such as chloroform, carbon tetrachloride, dichloromethane, and 1,2-dichloroethane were suitable for allylic alcohol formation, but in benzene, THF, and hexane solvents, α,β-unsaturated ketones became major products.[8] Use of the former solvents afforded a pyridine complex, $PdCl_2Py_2$, while in the latter solvents palladium black was precipitated. In the absence of pyridine, allylic alcohols were not formed. Use of poly(4-vinylpyridine)[9] in place of pyridine exhibited a similar yield of the allylic alcohol, and after the reaction a quantitative removal of palladium and molybdenum as polymer-bound complexes from the reaction solution was easily achieved by filtration.

In the absence of $MoO_2(acac)_2$, oxygenation products were formed in extremely low yield. This result indicates a Mo–OOBu-*t* intermediate acts as an active species.[10] Two or more mechanisms may be considered for the molybdenum-catalyzed hydroxylation of π-allylpalladium complexes. One mechanism involves a direct attack of the Mo–OOBu-*t* species on the π-allyl moiety from the Pd side. But it is probably excluded because of the steric hindrance around palladium atom. Another is a mechanism in which the Mo–OOBu-*t* species attacks the palladium atom directly to give a Pd^{II}–OOBu-*t* species or to give a Pd=O species derived from oxidation of Pd(II) to Pd(IV).[11] The resulting Pd–OOBu-*t*[12] or Pd=O intermediate intramolecularly oxidizes the π-allyl moiety, which leads regioselectively to allylic alcohol with internal hydroxyl.

This study may provide some information on the mechanism of heterogeneous allylic oxidation of olefins catalyzed by multicomponent metal oxides.[13]

Experimental Section

Proton NMR spectra were obtained on a Hitachi R-600, JEO-JNM 4H-100, or JNM FX-100 spectrometer; tetramethylsilane (Me_4Si) was used as the standard. Infrared spectra were recorded on a Hitachi EPI-G spectrophotometer. Gas chromatography (GLC) was performed on a Yanaco-G8 instrument by using a 3 m × 1.3 mm i.d. column packed with 3% silicone OV-17 on Celite or 20% PEG-20M on Celite. All π-allylpalladium complexes were prepared according to the method of Trost et al.[14] The originally prepared complex **4a** was obtained from α-ethylstyrene in a manner similar to that given above.

4a: mp 165–167 °C; NMR ($CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H, CH_3), 3.03 (s, 1 H, anti H of π-allyl moiety), 3.84 (s, 1 H, syn H), 4.03 (q, J = 6.6 Hz, 1 H), 7.2–7.5 (m, 5 H, phenyl). Anal. Calcd for $(C_{10}H_{11}ClPd)_2$: C, 44.00; H, 4.03; Cl, 12.99. Found: C, 43.99; H, 4.06; Cl, 13.47.

General Procedure for the Oxidation of π-Allylpalladium Complexes Catalyzed by $MoO_2(acac)_2$–*t*-BuOOH. A mixture of π-allylpalladium complex (0.3 mmol), $MoO_2(acac)_2$ (0.03 mmol), and pyridine (1.5 mmol) in 2 mL of chloroform-*d* was stirred at 60 °C for 10 min under a nitrogen atmosphere. To this solution was added *t*-BuOOH (0.36 mmol) in 2 mL of chloroform-*d* dropwisely during 15 min. The resulting solution was stirred at 60 °C for 24 h and then analyzed by GLC and NMR. A yellowish precipitate gradually separated from the reaction solution. This solid was collected by filtration and dried in vacuo to give ca. 60 mg of crude powder. It was recrystallized from dichloromethane to give yellow crystals of bis(pyridine)dichloropalladium ($PdCl_2Py_2$), mp 226–228 °C. Anal. Calcd for $C_{10}H_{10}N_2Cl_2Pd$: C, 35.81; H, 2.98; N, 8.35; Cl, 21.14. Found: C, 35.72; H, 2.89; N, 8.53; Cl, 21.09.

Conversion was determined by NMR and selectivity was determined by GLC. Yield is defined as multiplication of the conversion by the selectivity. All oxygenation products were collected by preparative GLC methods and identified by comparisons with authentic samples (retention time in GLC and NMR). NMR data of the compounds *trans*-pinocarveol (**1b**),[15] pinocarvone (**1c**),[15] 2-methylenecyclohexanol (**2b**),[16] 2-methylenecyclopentanol (**3b**),[17] and *trans*-5-*tert*-butyl-2-methylenecyclohexanol (**7b**)[18] were referred to those in the literature. For new compounds **4b** and **5b**, the structures were supported by the NMR spectroscopic data.

2-Phenyl-1-buten-3-ol (4b): NMR ($CDCl_3$) δ 1.32 (d, J = 6 Hz, 3 H, CH_3), 2.2–2.4 (br s, 1 H, OH), 4.85 (d, J = 6 Hz, 1 H, CHO), 5.31 (s, 1 H, =CH), 5.40 (s, 1 H, =CH), 7.4 (br s, 5 H, phenyl).

2-Propyl-1-penten-3-ol (5b): NMR ($CDCl_3$) δ 0.8–2.1 (m, 13 H, CH_3, CH_2 and OH), 3.98 (t, J = 6 Hz, 1 H, CHO), 4.84 (s, 1 H, =CH), 4.99 (s, 1 H, =CH).

Isolation of 2b. To a mixture of 4.63 g (19.5 mmol) of **2a**, 0.63 g (1.95 mmol) of $MoO_2(acac)_2$, and pyridine (7.7 g, 97 mmol) in chloroform (120 mL) was added 2.2 g of *t*-BuOOH in chloroform (100 mL) during 1 h. Stirring was continued at 60 °C for 24 h. The resulting mixture was filtered to remove the precipitate. The filtrate was treated with Na_2SO_3 solution and dried over anhydrous $MgSO_4$. After removal of solvent in vacuo, the residue was chromatographed on a Florisil column with petroleum ether (bp 40–60 °C) as the eluting solvent. In order to exclude remaining pyridine, the eluent was washed with dilute HCl solution, neutralized by $NaHCO_3$ solution, and dried over $MgSO_4$. From the solvent-evaporated residue, 925 mg of **2b** (42% yield) was isolated accompanied by a small amount of α,β-unsaturated ketone.

(7) On other nucleophiles: (a) Regioselectivity for nitrogen nucleophile attack has been studied by Stakem and Heck; secondary amines attack the less hindered side of π-allylic carbon rather than the more hindered one: Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584. (b) Trost and Keinan have reported that polymer-bound palladium species provide important enhanced stereoselectivity over the solubilized ones in allylic amination reaction: Trost, B. M.; Kelnan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. (c) The regioselectivity for AcO^- attack seems to be random (see ref 1b).

(8) In the latter solvents, allylic alcohols were detected at the initial stage of reaction, but they were probably dehydrogenated by palladium black to give α,β-unsaturated ketones.

(9) The copolymer of 4-vinylpyridine and divinylbenzene (96/4) was used.

(10) Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587.

(11) For the reaction of **1a** with iodosobenzene (PhIO) as an oxidant, oxygenation products **1b** (33% yield) and **1c** (8%) were obtained in dichloromethane solvent at ambient temperature. This fact suggests that the molybdenum-catalyzed oxidation of π-allylpalladium complex proceeds via the palladium–oxo (Pd=O) species. Groves et al. have reported that the metal–oxo species was prepared by PhIO oxidation: Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884 and references cited therein.

(12) In the oxidation of terminal olefins to methyl ketones by *t*-BuOOH, Mimoun proposed the mechanism involving the Pd^{II}–OOBu-*t* species: (a) Mimoun, H.; Charpentier, R.; Mitschler, A.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1980**, *102*, 1047. (b) Mimoun, H. *J. Mol. Catal.* **1980**, *7*, 1.

(13) In the allylic oxidation of olefins using Mo–Bi binary catalyst system, it is said that molecular oxygen initially attacks the Mo atom, followed by the transfer of the oxygen on Mo to Bi, and then oxygenation of the π-allyl moiety on Bi occurs. See: Matsuura, I. *Shokubai* **1979**, *21*, 409.

(14) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.

(15) Abraham, R. J.; Cooper, M. A.; Indyk, H.; Siverns, T. M.; Whittaker, D. *Org. Magn. Reson.* **1973**, *5*, 373.

(16) Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 2579.

(17) Kuivila, H. G.; Patnode, P. P. *J. Organomet. Chem.* **1977**, *129*, 145.

(18) Hoffman, R. W.; Goldmann, S.; Maak, N.; Gerlach, R.; Frickel, F.; Steinbach, G. *Chem. Ber.* **1980**, *113*, 819.

MCPBA Oxidation of π-Allylpalladium Complexes. π-Allylpalladium complex (0.3 mmol) was placed in the reaction vessel under a nitrogen atmosphere. Pyridine (1.5 mmol) in 2 mL of dichloromethane was introduced with stirring at 0 °C. MCPBA (0.36 mmol) in dichloromethane (3 mL) was added dropwise to the solution. The resulting mixture was stirred at 0 °C for 24 h, allowed to warm to ambient temperature, washed with Na_2SO_3 solution, $NaHCO_3$ solution, water, and brine, and dried on anhydrous $MgSO_4$. The solvent-evaporated residue was analyzed by GLC. Except for the cases of **1a** and **6a**, allylic alcohols were not detected and the isomers of allylic *m*-chlorobenzoates were obtained.

2-[(3-Chlorobenzoyl)oxy]-1-methylenecyclohexane (2e): IR (film) 1710, 1430, 1300, 1270, 1122, 1068, 896, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.4 (m, 8 H, CH_2), 4.81 (s, 1 H, =CH), 4.89 (s, 1 H, =CH), 5.4–5.7 (m, 1 H, CHO), 7.2–8.1 (m, 4 H, phenyl).

1-[[(3-Chlorobenzoyl)oxy]methyl]cyclohexene (2f): IR (film) 1715, 1430, 1295, 1260, 1122, 1070, 809, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.1 (m, 8 H, CH_2), 4.67 (s, 2 H, CHO), 5.81 (br s, 1 H, =CH), 7.2–8.1 (m, 4 H, phenyl).

2-[(3-Chlorobenzoyl)oxy]-1-methylenecyclopentane (3e): NMR ($CDCl_3$) δ 1.5–2.7 (m, 6 H, CH_2), 5.14 (s, 1 H, =CH), 5.25 (s, 1 H, =CH), 5.66 (m, 1 H, CHO), 7.3–8.1 (m, 4 H, phenyl).

1-[[(3-Chlorobenzoyl)oxy]methyl]cyclopentene (3f): NMR ($CDCl_3$) δ 1.8–2.6 (m, 6 H, CH_2), 4.87 (s, 2 H, CHO), 5.72 (br s, 1 H, =CH), 7.3–8.1 (m, 4 H, phenyl).

3-[(3-Chlorobenzoyl)oxy]-2-phenyl-1-butene (4e): IR (film) 1715, 1570, 1420, 1285, 1250, 1135, 1073, 908, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (d, J = 6.6 Hz, 3 H, CH_3), 5.35 (s, 1 H, =CH), 5.41 (s, 1 H, =CH), 6.06 (q, J = 6.6 Hz, 1 H, CHO), 7.2–8.1 (m, 9 H, phenyl).

1-[(3-Chlorobenzoyl)oxy]-2-phenyl-2-butene (4f): IR (film) 1720, 1570, 1420, 1280, 1250, 1135, 1073, 830, 749 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (d, J = 7 Hz, 3 H, CH_3), 5.00 (s, 2 H, CHO), 5.98 (q, J = 7 Hz, 1 H, =CH), 7.2–8.1 (m, 9 H, phenyl).

3-[(3-Chlorobenzoyl)oxy]-2-propyl-1-pentene (5e): IR (film) 1740, 1590, 1440, 1305, 1255, 1122 1070, 898, 749 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.2 (m, 12 H, CH_3 and CH_2), 4.95 (s, 1 H, =CH), 5.08 (s, 1 H, =CH), 5.38 (t, J = 6 Hz, CHO), 7.3–8.1 (m, 4 H, phenyl).

4-[[(3-Chlorobenzoyl)oxy]methyl]-3-heptene (5f): IR (film) 1730, 1585, 1440, 1305, 1250, 1125, 1070, 808, 750 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.3 (m, 12 H, CH_3 and CH_2), 4.73 (s, 2 H, CHO), 5.57 (t, J = 7 Hz, 1 H, =CH), 7.3–8.1 (m, 4 H, phenyl).

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Registry No. **1a**, 34829-33-9; **1b**, 1674-08-4; **1c**, 16812-40-1; **2a**, 53789-97-2; **2b**, 4065-80-9; **2e**, 84065-05-4; **2f**, 84065-06-5; **3a**, 53789-96-1; **3b**, 20461-31-8; **3e**, 84065-07-6; **3f**, 84065-08-7; **4a**, 31833-54-2; **4b**, 6249-81-6; **4e**, 84065-09-8; **4f**, 84065-10-1; **5a**, 54587-60-9; **5b**, 84065-11-2; **5e**, 84065-12-3; **5f**, 84065-13-4; **6a**, 12090-09-4; **6b**, 822-67-3; **6c**, 930-68-7; **6d**, 26828-73-9; **7a**, 55940-14-2; **7b**, 60041-30-7; MCPBA, 937-14-4; $MoO_2(acac)_2$, 17524-05-9; *t*-BuOOH, 75-91-2.

A Simple and Efficient Synthesis of L-Carnosine

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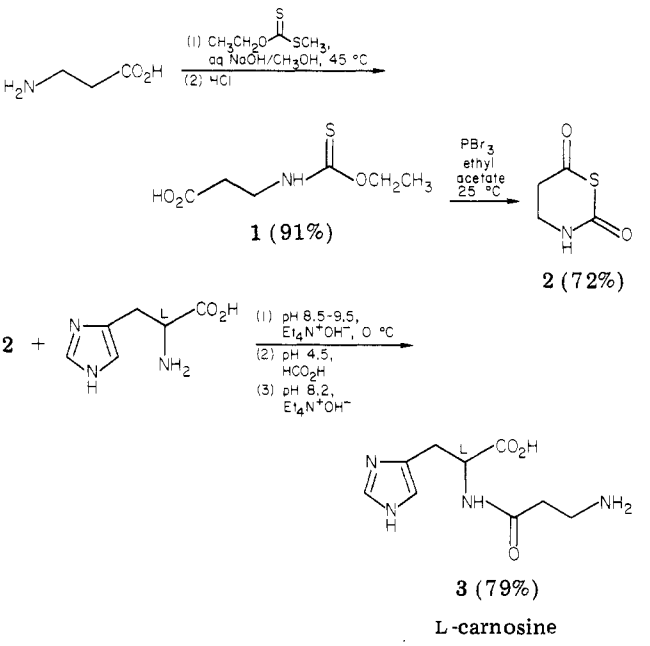
The naturally occurring dipeptide L-carnosine[1,2] (β-alanyl-L-histidine), **3**, is a substance of considerable biological and therapeutic importance. Recent studies[3] suggest that this material is an olfactory neurotransmitter. In addition, L-carnosine possesses the remarkable property of accelerating wound healing,[4] particularly when used following oral surgical procedures.

Scheme I



Previous syntheses of **3**[5] have, in general, required many steps and/or have afforded low overall yields of the final product. We now report a simple, short, high-yield preparation of **3** via the aqueous coupling of L-histidine and the *N*-(thiocarboxy) anhydride (NTA) of β-alanine, **2**.[6,7] This approach relies upon a new method for isolating water-soluble peptides from salt-containing aqueous reaction mixtures.

NTA's of amino acids have not enjoyed extensive utilization in peptide synthesis, principally because of their tendency to suffer some degree of racemization in the coupling process.[6] However, β-alanine, a material without

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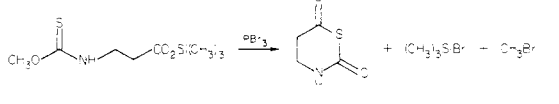
(7) Kricheldorf, H. *Chem. Ber.* **1971**, *104*, 3146. Kricheldorf has prepared β-alanine NTA by the reaction of *N*-(methoxythiocarbonyl) β-alanine trimethylsilyl ester with PBr_3:



The use of this NTA in a peptide coupling reaction has not been reported.

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