Further Studies on the Ring Transformation of Pyrimido[5,4-*e*]-*as*-triazine 4-Oxides to Pyrrolo[3,2-*d*]pyrimidines Involving 1,3-Dipolar Cycloaddition Reactions

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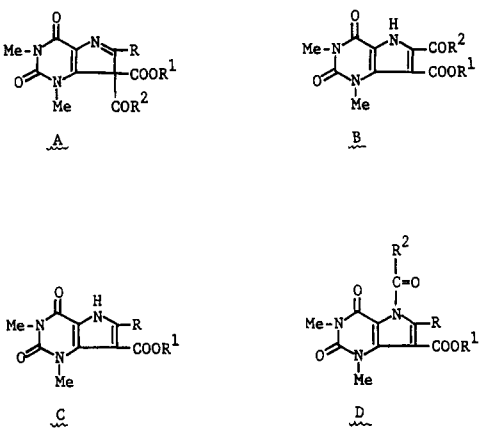
The reaction of 3-alkyl(or aryl)-6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-oxides (**1a–f**) with ethyl phenylpropiolate (EPP) in toluene afforded the unexpected 6-alkyl(or aryl)-5-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**7a–f**). The structures of **7a–f** were supported by the spectral data as well as by the chemical means and were confirmed by the single-crystal X-ray diffractions. On the other hand, the reaction of 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-oxide (**1g**) with EPP yielded 6-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**9**).

We have previously reported that the 1,3-dipolar cycloaddition reactions of fervenulin 4-oxides, 6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione 4-oxides (**1**), with acetylenic esters, i.e., dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate (MP), result in a new ring transformation of the π-deficient *as*-triazine nucleus to give a variety of pyrrolo[3,2-*d*]pyrimidines (9-deazapurines), e.g., B and C in Chart I, depending on the dipolarophile and solvent employed as well as on the substituent at the 3-position of **1**.[1]

Possible mechanisms have been suggested for this unique ring transformation, however none of the intermediates could be isolated probably because of their high reactivity due to the multifunctionalized structures. Among several plausible intermediates, the most important intermediate determining the final products, e.g., B and C, is believed to be the 7-H pyrrolopyrimidine A. Namely, the intermediate A where R = H would cause a 1,5-sigmatropic rearrangement of the COR^2 group to give B, while A, R = alkyl or aryl would undergo hydrolytic cleavage of the COR^2 group to give C.

In connection with these findings and with current medicinal interest in pyrrolo[3,2-*d*]pyrimidines,[2] we now have further investigated the reaction of **1** with ethyl phenylpropiolate (EPP) in hope of isolating the intermediate A since this reagent can be regarded as a less reactive dipolarophile than DMAD or MP. However, we have found that the products obtained are the unexpected pyrrolopyrimidines D which would arise from a novel 1,5-sigmatropic rearrangement of the COR^2 group of A. The present paper deals with the synthesis of a series of D and their structural elucidation by spectral and chemical as well as by single-crystal X-ray diffraction studies.

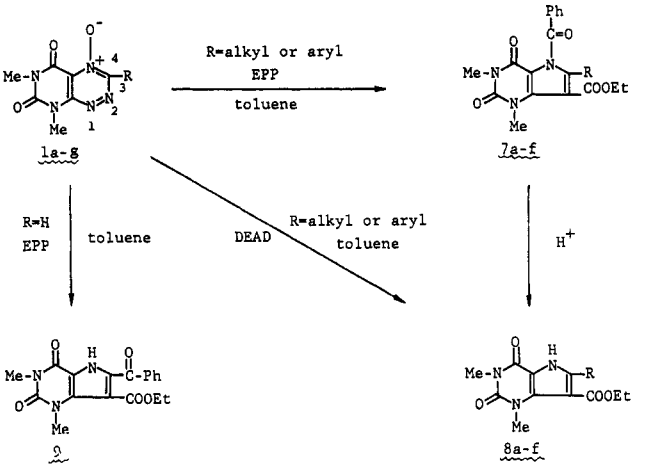
Chart I



Results and Discussion

As shown in Scheme I, heating of 3-methylfervenulin 4-oxide (**1a**)[1] with 2 equiv of EPP in dry toluene at 120 °C for 2 h resulted in the isolation of 5-benzoyl-7-(ethoxycarbonyl)-1,3,6-trimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**7a**) in 54% yield. The reaction of 3-ethylfervenulin 4-oxide (**1b**) with EPP likewise gave the corresponding pyrrolopyrimidine (**7b**) in similar yield. The reaction was equally applicable to 3-arylfervenulin 4-oxides (**1c–f**)[4] to yield the corresponding 6-aryl-5-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidines (**7c–f**) in 21–62% yields along with the respective deoxygenated 3-arylfervenulins (**10c–f**).[4] In general, the pyr-

Scheme I[a]



[a] a, R = Me; b, R = Et; c, R = Ph; d, R = 4-ClC_6H_4; e, R = 4-MeC_6H_4; f, R = 4-$NO_2C_6H_4$; g, R = H.

(1) Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.* **1979**, *44*, 3830.
(2) For a review on the pyrrolo[3,2-*d*]pyrimidines, see: Amarnath, V.; Madhav, R. *Synthesis* **1974**, 837. For recent advances on this ring system, see ref 1 and references cited therein.
(3) The compound **1c** was prepared by the method described in ref 1 and the compounds **1d–f** were synthesized by the reported procedure: Yoneda, F.; Nagamatsu, T.; Shinomura, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 713. The melting point and yield of new compound **1e** are as follows: mp 262–264 °C (from DMF), 75%.
(4) Senga, K.; Ichiba, M.; Kanamori, Y.; Nishigaki, S. *Heterocycles* **1978**, *9*, 29.

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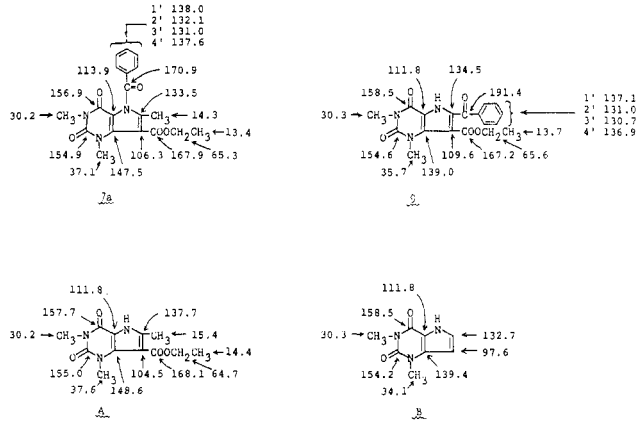
Table I. Pyrrolo[3,2-*d*]pyrimidines (7 and 8)[a]

	compd 7[b]		compd 8[b]	
	yield, %	mp, °C	yield, %	mp, °C
a	54	157–159	79[c]	249–250
			72[d]	
b	52	125–128	95[c]	222–223
			73[d]	
c	21	165–166	43[c]	258–259
			53[d]	
d	62	212–213	79[c]	282–284
			75[d]	
e	52	226–228	97[c]	227–230
			78[d]	
f	21	181–182	95[c]	>300
			91[d]	

[a] Satisfactory analytical data (± 0.4% for C, H, and N) were reported for all compounds in the table. [b] All compounds were recrystallized from EtOH. [c] Yield by the acid hydrolysis of **7a–f**. [d] Yield by the reaction of **1a–f** with diethyl acetylenedicarboxylate.

Chart II[a]



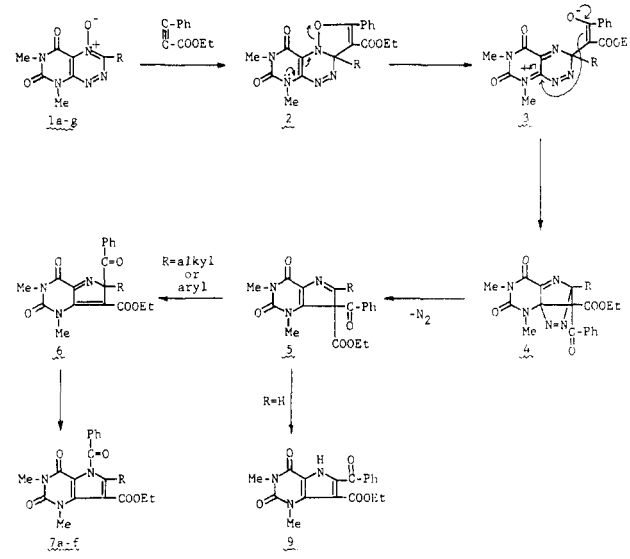
[a] The ^{13}C NMR chemical shifts of pyrrolo [3,2-*d*]-pyrimidines in Me_2SO-d_6 are given in δ units. The chemical shifts of compounds A and B[1] are also cited for references.

rolopyrimidines were readily precipitated out from the reaction mixture and the deoxygenated fervenulins were obtained by concentration of the filtrate (Table I).

The structures of **7a–f** were tentatively assigned by analytical and spectral data (IR, ^1H NMR, UV, and MS). Particularly, the IR and ^1H NMR spectra did not indicate the presence of a secondary amino group on the pyrrole nucleus, and the mass spectra revealed the strong parent ions as well as the characteristic $M^+ - 105$ and $M^+ - 45$ fragment ions corresponding to the elimination of a benzoyl and an ethoxy radical, respectively. Moreover, as depicted in Chart II, the ^{13}C NMR (CF_3COOH) spectrum of **7a** showed a signal at 170.9 ppm which is attributable to a carbonyl carbon of the benzamide structure and any signal corresponding to the sp^3 carbon on the pyrrole nucleus expected for the structure **5** or **6** could be observed.

Additional support for the structures of **7a–f** was derived from their susceptibility toward hydrolysis. For example, heating of the respective **7a–f** with 10% ethanolic HCl gave the corresponding 6-alkyl(or aryl)-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones (**8a–f**) in 43–95% yields. Furthermore, heating of **7a–f** in protic solvents, e.g., H_2O, MeOH, and EtOH, for a prolonged period also afforded **8a–f**.[5] The compounds **8a–f** were identical with the product obtained

Scheme II



by the reaction of the appropriate **1a–f** with diethyl acetylenedicarboxylate (DEAD) in dry toluene at 95 °C for 30 min.

The spectral data and the susceptibility toward hydrolysis suggested the structures indicated, however, these results could not unequivocally exclude the possibility of an alternative structure, i.e., **5** or **6** in Scheme II (vide infra). Consequently, rigorous structural proof of **7** was accomplished by using single-crystal X-ray diffractions on the compounds **7a** and **7c**. As depicted in Figures 1 and 2, the ORTEP[6] drawings clearly indicated that the benzoyl group is located at the position N-5 in each case and the possibility of the alternative structures such as **5** and **6** was eliminated. The intermediates **5** and **6** seem to be less stable than **7** because of the steric hindrance due to the bulky benzoyl group. The crystal data and fractional coordinates with equivalent isotropic thermal parameters were summarized in Tables II–V.

In contrast to the reaction of **1a–f** with EPP, the treatment of fervenulin 4-oxide (**1g**) with EPP in dry toluene at 95 °C for 1 h resulted in the isolation of 6-benzoyl-7-(methoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**9**) in 82% yield and the expected 5-benzoylpyrrolopyrimidine could not be obtained. The structure of **9** was suggested by the presence of a secondary amino group and a benzoyl group in the ^1H NMR spectrum. Moreover, the carbonyl carbon of the benzoyl group was observed at 191.4 ppm in the ^{13}C NMR (CF_3COOH) spectrum (Chart II).

As shown in Scheme II, the reaction of **1a–f** with EPP leading to **7a–f** can be best explained in terms of the initial formation of the adduct (**2**) by the 1,3-dipolar cycloaddition reaction. The cleavage of the isoxazoline nucleus of **2** to the dipolar intermediate (**3**), followed by the intramolecular cyclization to **4**, and subsequent extrusion of N_2 would give the 7-H pyrrolopyrimidine intermediate **5**. The 1,5-sigmatropic rearrangement of the benzoyl group of **5** would then give the final products via the 6-H pyrrolopyrimidine intermediate **6**. The deoxygenations of **1c–f** into **10c–f** would proceed by the thermal oxidative process.[7] On the contrary to **1a–f**, the reaction of **1g** with EPP leading to **9** can be rationalized by assuming the 1,5-sigmatropic re-

(5) The hydrolytic debenzoylation also proceeded gradually during the storage.

(6) Johnson, C. K. "ORTEP"; Report ORNL-3794, Oak Ridge National Laboratory, TN, 1965.

(7) Katritzky, A. R.; Lagowski, J. M. "Chemistry of Heterocyclic N-Oxides"; Academic Press: New York, 1971; pp 229–231.

arrangement of the benzoyl group of **5**.

Experimental Section

Melting points were taken on a YANACO micro-hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR A-100 spectrophotometer from samples mulled in Nujol. ^{1}H NMR spectra were determined at 90 MHz with a Varian EM-390 spectrometer with tetramethylsilane as the internal standard. ^{13}C NMR spectra were performed on a JEOL JMS-PS-100 spectrometer by using tetramethylsilane as the internal standard. UV spectra were performed on a Hitachi 124 spectrophotometer. The molecular weight for all compounds were correctly analyzed by the mass spectroscopy with a JEOL JMS D-300 spectrometer by a direct inlet system at 70 eV. Elemental analyses (C, H, and N) for all new compounds were in agreement with the assigned structures to within ±0.4%. Results of elemental analyses were made available to the editor.

6-Alkyl(or Aryl)-5-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (7a–f). A mixture of the appropriate 3-alkyl(or aryl)fervenulin 4-oxides (**1a–f**)[1] (0.001 mol) and ethyl phenylpropiolate (0.002 mol) in dry toluene (10 mL) was heated at 120 °C for 3 h with stirring. After cooling, the precipitates were filtered, washed with EtOH, and recrystallized from EtOH to give the corresponding **7a–f**.

Typical examples of ^{1}H NMR and UV data of these products are as follows.

7a: ^{1}H NMR (Me_2SO-d_6) δ 1.33 (t, 3 H, Me, J = 7 Hz), 2.71 (s, 3 H, NMe), 3.10 (s, 3 H, 5-Me), 3.51 (s, 3 H, NMe), 4.38 (q, 2 H, CH_2, J = 7 Hz), 7.65 (m, 5 H, C_6H_5); UV (EtOH) λ_{max} 230 nm (log ε 3.98), 250 (3.82), 275 (3.59).

7c: ^{1}H NMR (Me_2SO-d_6) δ 0.86 (t, 3 H, Me, J = 7 Hz), 3.18 (s, 3 H, NMe), 3.55 (s, 3 H, NMe), 4.02 (q, 2 H, CH_2, J = 7 Hz), 7.33–7.56 (m, 10 H, two C_6H_5); UV (EtOH) λ_{max} 235 nm (log ε 4.76), 250 (4.71), 280 (4.48).

The reaction filtrate which removed **7c–f** was evaporated in vacuo, and the residue was covered with EtOH (10 mL). The insoluble material was filtered and recrystallized from EtOH to give the respective 3-arylfervenulins (**10c–f**), which were identical with the authentic samples.[4] The yields of **10c–f** are as follows: **10c** (19%); **10d** (13%); **10e** (28%); **10f** (67%).

6-Alkyl(or Aryl)-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (8a–f). Method A. A suspension of the appropriate **7a–f** (0.0002 mol) in a mixture of 10% HCl (3 mL) and EtOH (3 mL) was refluxed for 1.5 h. After cooling, the precipitates were filtered, washed with H_2O, dried, and recrystallized from EtOH to give the corresponding **8a–f**.

Typical examples of ^{1}H NMR and UV data of these products are as follows.

8a: ^{1}H NMR (Me_2SO-d_6) δ 1.30 (t, 3 H, Me, J = 7 Hz), 2.41 (t, 3 H, Me, J = 7 Hz), 3.23 (s, 3 H, NMe), 3.51 (s, 3 H, NMe), 4.25 (q, 2 H, CH_2, J = 7 Hz), 12.52 (br, 1 H, NH, D_2O exchangeable); UV (EtOH) λ_{max} 233 nm (log ε 4.38), 273 (3.86).

8c: ^{1}H NMR (Me_2SO-d_6) δ 1.02 (t, 3 H, Me, J = 7 Hz), 3.28 (s, 3 H, NMe), 3.47 (s, 3 H, NMe), 4.10 (q, 2 H, CH_2, J = 7 Hz), 7.47 (s, 5 H, C_6H_5), 12.66 (br, 1 H, NH, D_2O exchangeable); UV (EtOH) λ_{max} 235 nm (log ε 4.65), 290 (4.44).

Method B. A mixture of the appropriate **1a–f** (0.0002 mol) and diethyl acetylenedicarboxylate (0.00024 mol) in dry toluene (3 mL) was heated at 95 °C for 30 min with stirring. After cooling, the precipitates were filtered, washed with EtOH, and recrystallized from EtOH to give the corresponding **8a–f**, identical with the compounds obtained by the Method A.

6-Benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9). A mixture of fervenulin 4-oxide (**1g**)[1] (0.052 g, 0.00025 mol) and ethyl phenylpropiolate (0.052 g, 0.0003 mol) in toluene (3 mL) was heated at 95 °C for 1 h with stirring. After cooling, the precipitates were filtered, washed with EtOH, and recrystallized from EtOH to give **9**: 0.073 g (82%); mp 217–219 °C; ^{1}H NMR (Me_2SO-d_6) δ 0.81 (t, 3 H, Me, J = 7 Hz), 3.30 (s, 3 H, NMe), 3.56 (s, 3 H, NMe), 3.76 (q, 2 H, CH_2, J = 7 Hz), 7.33–7.92 (m, 5 H, C_6H_5), 13.50 (br, 1 H, NH, D_2O exchangeable); UV (EtOH) λ_{max} 225 nm (log ε 4.68), 252 (4.48), 290 (4.05), 325 (3.85).

X-ray Crystallographic Analysis of 7a. A single crystal (colorless plate) of **7a** was obtained by slow evaporation of a benzene solution. The crystal data and fractional coordinates with equivalent isotropic thermal parameters are summarized in Tables II and III.

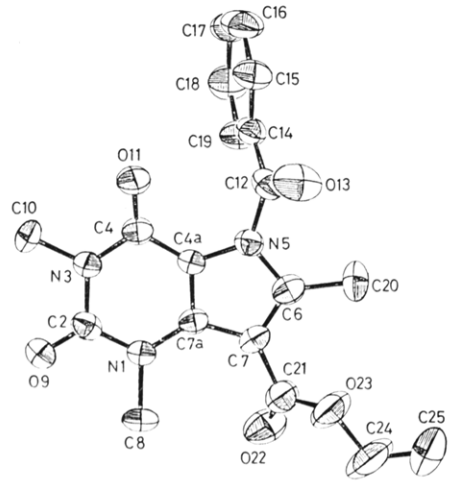


Figure 1. An ORTEP[6] drawing of **7a** with thermal ellipsoids at the 50% probability level.

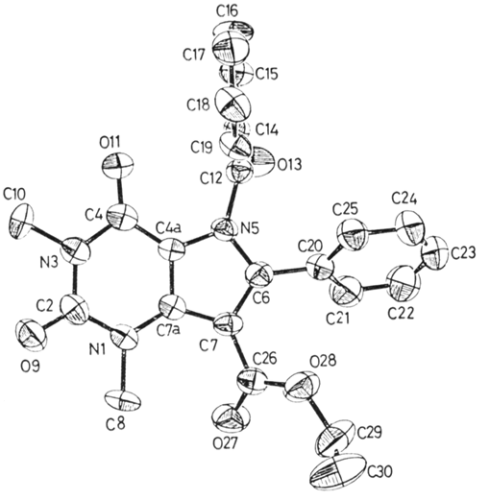


Figure 2. An ORTEP[6] drawing of **7c** with thermal ellipsoids at the 50% probability level.

The lattice constants and intensity data were measured by using graphite-monochromated Mo Kα radiation (λ 0.70926 Å) on a Rigaku AFC-5 four-circle diffractometer at 298 K. A total of 1516 unique reflections with $|F°| > 3\sigma(|F°|)$ were obtained by using the $\theta - 2\theta$ scanning method with 2θ scan speed of 4°/min up to 2θ = 50°. The structure was solved by the direct method with the MULTAN 78 program[8] and refined by the full-matrix least-squares program LINUS.[9] The structure of **7a** is shown in Figure 1.[10]

X-ray Crystallographic Analysis of 7c. A single crystal (colorless plate) of **7c** was obtained by slow evaporation of a benzene solution. The crystal data and fractional coordinates with equivalent isotropic thermal parameters are summarized in Tables IV and V.

Analytical conditions were as described for **7a**. The structure was determined by a combination of direct and Fourier methods and refined to an R value of 0.051 for 1490 observed reflections [$|F°| > 3\sigma(|F°|)$]. The structure of **7c** is shown in Figure 2.[10] All numerical calculations were performed on a HITAC M-200H Computer at the Computer Center, University of Tokyo.

(8) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. "MULTAN 78 A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; Universities of York, England, and Louvain, Belgium, 1978.

(9) Coppens, P.; Hamilton, W. C. *Acta Crystallogr., Sect. A* **1970**, *26*, 71.

(10) Further crystallographic details are available as Supplementary Material.

Acknowledgment. We are grateful to Drs. K. Nagahara and Y. Okamoto of Kitasato University for helpful discussions on ^{13}C NMR spectra. We also thank Dr. K. Saito and H. Yamanaka of this school for measurement of mass spectra. A part of this work was supported by a Grant-in-Aid from Tokyo Biochemical Foundation.

Registry No. **1a**, 60026-36-0; **1b**, 63069-55-6; **1c**, 41661-91-0; **1d**, 59776-20-4; **1e**, 96429-52-6; **1f**, 59776-21-5; **1g**, 62758-20-7; **7a**, 96429-53-7; **7b**, 96429-54-8; **7c**, 96429-55-9; **7d**, 96429-56-0; **7e**, 96429-57-1; **7f**, 96429-58-2; **8a**, 96429-59-3; **8b**, 96429-60-6; **8c**, 96429-61-7; **8d**, 96429-62-8; **8e**, 96429-63-9; **8f**, 96429-64-0; **9**, 96429-65-1; **10c**, 25696-85-9; **10d**, 30561-26-3; **10e**, 65358-01-2; **10f**, 25775-01-3; diethyl acetylenedicarboxylate, 762-21-0; ethyl phenylpropiolate, 2216-94-6.

Supplementary Material Available: Tables of atomic coordinates, anisotropic temperature factors, bond distances and angles, and least-square planes for **7a** and **7c** (10 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of Tetrahydrofurans and Tetrahydropyrans Using Thallium(III)-Induced Cyclizations

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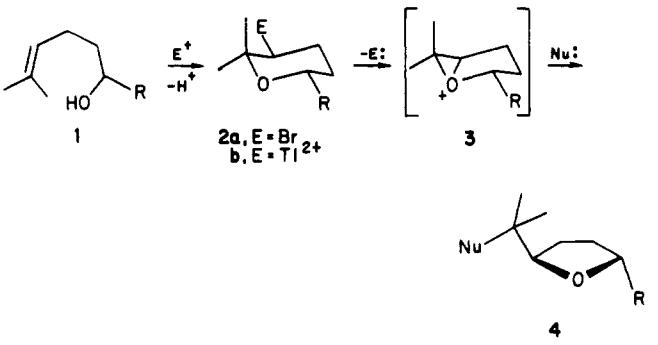
Various substituted 4-alkenols undergo electrophilic cyclization with thallium(III) salts in a regio- and stereoselective manner. The organothallium intermediate is not isolated but undergoes dethallation with concomitant 1,2-oxygen migration, leading to ring-expanded or -contracted products. The method constitutes a particularly efficient, one-step procedure for the synthesis of trans-2,5-disubstituted tetrahydrofurans (e.g., 1 → 4). In these cases stereochemical control in the attachment of nucleophiles to the side chain is also manifested. In general, the method is less effective for formation of tetrahydropyrans by the ring-expansion mechanism or when severe 1,3-diaxial interactions are developed during cyclizations to six-membered rings (e.g., with substrates 11 and 12). When *trans*-2-allylcyclohexanols are employed as substrates, 6,6- or 6,5-fused bicyclic ethers are formed with good stereochemical control and with a regiospecificity that can be manipulated in a Markovnikov fashion (e.g., 39 → 40 or 41).

In our continuing efforts[2] to devise stereochemically unambiguous syntheses of five- and six-membered cyclic ethers, common structural subunits in a wide variety of natural products,[3] we recently reported a two-step preparation of trans-2,5-disubstituted tetrahydrofurans 4.[2d] The sequence involved bromocyclization of 4-alkenols 1 to give the tetrahydropyrans **2a** and subsequent silver ion induced ring contraction, presumably by way of the bridged oxonium cations **3** (Scheme I). The stereochemistry is dictated from the outset by the equatorial preference of R in the chair-like transition state that leads to tetrahydropyran formation, and it is preserved in the subsequent ring contraction. Although highly stereoselective, the initial cyclization reaction produces varying amounts of the undesired tetrahydrofuran regioisomer, depending on the particular substitution pattern and polarization of the double bond.

We now report an improvement in this strategy which accomplishes the transformation of **1** to **4** regiospecifically and in a single step. The key to success lies in the use of thallium(III) salts as the electrophilic reagents. We reasoned that thallium, together with its accompanying counterions, should be much more sterically demanding than bromine and hence show a greater propensity for inducing cyclization to the tetrahydropyran regioisomer

Scheme I



2b. The greater sensitivity to the intramolecular participation of a hydroxyl group that electrophilic attack by thallium(III)[4a] shows in comparison to bromine[4b] should also favor stereocontrol as well as regiocontrol. Most importantly, the well-documented nucleofugality of thallium(III) should lead to the spontaneous decomposition of **2b**, the ring oxygen atom being ideally placed to assist in displacing the departing thallium(I) species and to stabilize the carbocation formally produced. As in our previous synthesis, bridged oxonium ions **3** are the putative intermediates, solvolysis of which produces the desired trans-2,5-disubstituted tetrahydrofurans **4**.

Examples of the oxythallation of alkenes with intramolecular nucleophilic participation are less common than might be expected,[5] especially when compared to the iso-

(1) On leave from the Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa.

(2) (a) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. (b) Bartlett, P. A.; Holmes, C. P. *Tetrahedron Lett.* **1983**, *24*, 1365. (c) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (d) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668.

(3) (a) Wierenga, W. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, pp 287–294, 299–325. (b) Westley, J. W., Ed. "Polyether Antibiotics: Naturally Occurring Acid Ionophores"; Marcel Dekker: New York, 1982; 2 Vols.

(4) (a) Byrd, J. E.; Halpern, J. *J. Am. Chem. Soc.* **1973**, *95*, 2586. (b) Williams, D. L. H.; Bienvenüe-Goetz, E.; Dubois, J. E. *J. Chem. Soc. B* **1969**, 517.

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