mmol) and *tert*-butyl acrylate (30 mL, 205 mmol) was stirred for 8 days under an argon atmosphere in the dark at which time TLC (2:1 hexanes/EtOAc) showed 2 spots, $R_f$ = 0.13 (major, corresponding the $\beta$-addition product) and $R_f$ = 0.07 (minor, corresponding to unreacted **14**). The *tert*-butyl acrylate was removed in vacuo, and the residue was purified by radial chromatography (2:1 hexanes/EtOAc) to afford unreacted starting material (138 mg, 0.41 mmol) and **15** (418 mg, 0.91 mmol, 51%) [65% based upon recovered starting material] as a clear oil, which solidified on standing: mp 61-62 °C; $[\alpha]_D$ = -43.7° ($c$ = 2, $CH_2Cl_2$); IR ($CHCl_3$) 3028, 3011, 1724 (br), 1378, 1258, 1216, 1156, 910 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 80 °C) $\delta$ 1.39 (s, 9 H, *t*-Bu), 2.20 (sym 6 lines, 1 H, H-4*S*), 2.27 (t, 2 H, $J$ = 6.7 Hz, $CH_2$COO*t*-Bu), 2.66 (sym 6 lines, 1 H, H-4*R*), 2.84 (br m, 2 H, H-5), 3.03 (m, 2 H, partially obscured by $H_2O$, NHC$H_2$CH$_2$), 3.40 (br s, 1 H, H-2), 3.82 (AB q, 2 H, $J$ = 13.4 Hz, NC$H_2$Ph), 4.33 (br t, 1 H, H-3), 5.13 (s, 2 H, OC$H_2$Ph), 7.21-7.34 (m, 10 H, Ph); {$^1$H}$^{13}$C NMR ($CDCl_3$) $\delta$ 28.1, 31.0 (br), 36.5, 44.2, 54.2 (br), 62.0 (br), 64.2 (br), 66.7, 78.0 (br), 127.4, 128.2, 128.4, 128.5, 129.1, 135.7 (br), 171.7, 172.7; MS $m/z$ 454 (M$^+$, <0.005), 381 (M$^+$ - O-*t*-Bu, 4.2), 329, 162, 120, 91 (100); accurate mass 454.2465, calcd for $C_{26}H_{34}N_2O_5$ 454.2468, (M$^+$ - O-*t*-Bu) accurate mass 381.1821, calcd for $C_{22}H_{25}N_2O_4$ 381.1814.

**(*S*)-(2-Benzyl-(5*R*)-isoxazolidin-5-yl)(2-oxoazetidin-1-yl)acetic Acid Benzyl Ester (16).** A solution of **15** (481 mg, 0.91 mmol) and trifluoroacetic acid (TFA, 12 mL; freshly distilled from $P_2O_5$) was stirred under argon at room temperature for 15 min, and the TFA was removed in vacuo. The unstable clear oil thus obtained was dried under vacuum for 0.5 h and used directly in the next reaction.

A solution of the $\beta$-amino acid in acetonitrile (150 mL) was treated with triphenylphosphine (300 mg, 1.1 mmol, 1.2 equiv) and dipyridyl disulfide (250 mg, 1.1 mmol, 1.2 equiv). The mixture was heated at reflux for 18 h, cooled to room temperature, and concentrated in vacuo, and the product was separated from the triphenylphosphine, triphenylphosphine oxide, and 2-mercaptopyridine by repeated radial chromatography (1:1 hexanes/EtOAc, $R_f$ = 0.13, followed by 1:1 $CH_2Cl_2/Et_2O$ for separation from the 2-mercaptopyridine) to afford **16** (159 mg, 0.42 mmol, 46% through 2 steps) as a slightly yellow oil: $[\alpha]_D$ = -30° ($c$ = 2.0, $CH_2Cl_2$); IR ($CHCl_3$) 3012, 2919, 1739 (br), 971 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 80 °C) $\delta$ 2.05 (sym 6 lines, 1 H, H-4*S*), 2.43 (sym 6 lines, 1 H, H-4*R*), 2.85 (br m, 2 H, H-3'), 2.87-2.90 (br m, 1 H, H-5), 2.93-2.97 (br m, 1 H, H-5), 3.36 (br m, 2 H, H-4'), 3.89 (s, 2 H, NC$H_2$Ph), 4.53 (d, 1 H, $J$ = 5.12 Hz, H-2), 4.57 (sym app 3 line m, 1 H, H-3), 5.17 (s, 2 H, OC$H_2$Ph), 7.21-7.38 (m, 10 H, Ph); {$^1$H}$^{13}$C NMR ($CDCl_3$) $\delta$ 31.6, 37.2, 40.2, 54.4, 56.4, 62.1 (br), 67.3, 75.8, 127.5, 128.1, 128.3, 128.5, 128.6, 129.1, 135.1, 136.8, 168.9, 177.7; MS $m/z$ 380 (M$^+$, 5.4), 289, 162, 120, 91 (100); accurate mass 380.1740, calcd for $C_{22}H_{24}N_2O_4$ 380.1736.

**(2*S*,3*R*)-5-Amino-3-hydroxy-2-(2-oxoazetin-1-yl)pentanoic Acid (17, Proclavaminic Acid).** To a 250-mL Parr hydrogenation bottle was added L-*threo*-isoxazolidine **16** (82 mg, 0.22 mmol), absolute ethanol (8 mL), water (8 mL), and 20% $Pd(OH)_2$/C (160 mg, Pearlmans catalyst). The mixture was degassed and mechanically shaken under an atmosphere of hydrogen (initially 50 psi, Parr hydrogenation apparatus) for 2 days. The mixture was filtered through a bed of Celite to remove the catalyst, rinsing with water (50 mL). The filtrate was lyophylized to afford a slightly brown powder, which was purified by preparative HPLC (Whatman ODS-3 C18 R.P.; 9.4 × 250 mm; detection at 220 nm; mobile phase: $H_2O$, 3.0 mL/min; retention time, 4.1 min) to afford **17** (38.0 mg, 0.19 mmole; 85%) as clear white prisms after lyophilization: mp 127-130 °C (dec with gas evolution); $[\alpha]_D$ = +7.3° ($c$ = 1.3, $H_2O$); IR (1% in KBr) 3373, 2940 (v br), 2088, 1703 (br), 1634 (br), 1378, 773 cm$^{-1}$; $^1$H NMR ($D_2O$) $\delta$ 1.77 (m, 2 H, H-4), 2.93 (t, $J$ = 3.97 Hz, 2 H, H-3'), 3.07 (m, 2 H, C$H_2$NH$_2$), 3.43 (m, 1 H, H-4'), 3.50 (m, 1 H, H-4'), 4.00 (d, $J$ = 5.5 Hz, 1 H, H-2), 4.22 (m, 1 H, H-3); {$^1$H}$^{13}$C NMR ($D_2O$, dioxane internal reference at 67.4 ppm) $\delta$ 31.68, 36.16, 37.89, 41.02, 63.27, 69.61, 172.83, 174.89; CIMS $m/z$ 203 (MH$^+$, 100; methane as reagent gas), 185, 167, 143, 115; accurate mass (MH$^+$) 203.1037, calcd for $C_8H_{15}N_2O_4$ 203.1037.

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**Registry No.** **2**, 58001-44-8; **7** (R = Bn, R' = Cbz), 3705-42-8; **8**, 130096-70-7; **9**, 74635-18-0; **10**, 130096-71-8; **11**, 130096-72-9; **12**, 107942-04-1; **13**, 107942-03-0; **14**, 130096-73-0; **15**, 130096-74-1; **16**, 130096-75-2; **17**, 112240-59-2; $H_2C$=CHCOOBu-*t*, 1663-39-4; BnNHOH, 622-30-0.

**Supplementary Material Available:** $^1$H and $^{13}$C NMR spectra for **10**, **11**, and **14-17** (12 pages). Ordering information is given on any current masthead page.

# Nucleophile-Dependent Substitution Reactions of 5-Halovaleric Acid Esters: Synthesis of 6,12-Dioxamyristic Acid

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The reaction of 5-ethoxypentan-1-ol with a variety of 5-halovalerate alkyl esters afforded ester exchange products rather than the expected products of Williamson ether synthesis. The virtually unknown reaction of an alkoxide with a 5-halovalerate ester contrasts strongly with literature reports of reactions involving other nucleophiles in which the halogen substitution products are nearly always isolated. An explanation is offered for this behavior in terms of a chelation-induced conformation of the substrate. Although the direct synthetic approach failed, the hitherto unknown title compound could still be prepared, albeit in six steps in 6% overall yield. The approach used is discussed along with the interesting chemistry of this system.

Myristoyl-CoA:protein *N*-myristoyl transferase (NMT, E.C. 2.3.1.97) catalyzes the co-translational attachment of myristate via an amide bond to the $NH_2$-terminal glycine residues of a number of cellular and viral proteins (reviewed in ref 1). *N*-Myristoylation of certain retroviral

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(1) Towler, D. A.; Gordon, J. I.; Adams, S. P.; Glaser, L. *Ann. Rev. Biochem.* **1988**, *57*, 69.

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**Table I. Reactions of Nucleophiles with Alkyl 5-Halovalerates**

| heteronucleophile used | alkyl group in ester | 5-X | yield, % | ref |
|---|---|---|---|---|
| imidazole$^-$ | $CH(C_6H_5)_2$ | Br | 93 | 16 |
| NaCN | $CH_2CH_3$ | Cl | 76 | 17 |
| $ArS^-$ | $CH_3$ | Br | 95 | 18 |
| $C_6H_5O^-$ | $CH_2CH_3$ | Br | 91 | 19 |

gag polyprotein precursors, including the $Pr^{55gag}$ encoded by the human immunodeficiency virus I, is necessary for viral assembly.[2] We have synthesized analogues of myristic acid in which one or more methylene groups were replaced by oxygen atoms.[3,4] These analogues have reduced hydrophobicity relative to myristic acid but have similar chain lengths.[3] When converted to their coenzyme A derivatives, they serve as substrates for the enzyme.[3] These analogues represent a means to assess the physical chemical properties of myristate which are important not only for its interaction with the acylCoA binding site of the NMT but also for the biological function of the proteins to which it is attached.[5] During the course of a more complete study of multiple oxygen containing analogues of myristic acid,[4] we encountered considerable difficulty in the preparation of one analogue: 6,12-dioxamyristic acid, 1. In the present report, we note that the specific problem represents a phenomenon of more general interest.

$$CH_3CH_2O(CH_2)_5O(CH_2)_4COOH\ (1)$$

## Results and Discussion

Two nucleophilic substitution pathways are available to halovalerate esters: displacement at the 5-carbon bearing the halogen leaving group or addition (addition–elimination) to the carbonyl group. Reaction proceeding by the former pathway (pathway A) would afford a 5-substituted valerate ester, and the latter pathway would afford a new 5-halovalerate ester. The possible pathways are

$$X(CH_2)_4COOR + Nu^- \rightarrow Nu(CH_2)_4COOR\ (A) + X(CH_2)COONu\ (B)$$

**Attempted Synthesis of 6,12-Dioxamyristic Acid.** At the outset, we planned to prepare 6,12-dioxamyristic acid as outlined below. First, pentane-1,5-diol would be protected as its tetrahydropyranyl ether, alkylated, and deprotected, and the 5-ethoxypentanol would then be alkylated using alkyl 5-bromovalerate. Substitution reactions involving nearly a dozen different nucleophiles[6-15] with 5-halovalerate esters have been reported and, with a single exception,[6] attack at the 5-carbon and displacement of halogen is observed (see Table I). To our knowledge, however, no report has appeared of any substitution involving alkoxide ion (the Williamson ether synthesis) with an alkyl 5-halovalerate.

**Oxygen Nucleophiles.** When we attempted the base-catalyzed reaction between 5-ethoxypentan-1-ol and various alkyl 5-halovalerates, the only product isolated resulted from ester exchange rather than nucleophilic substitution at the 5-position. With NaH and tetrahydrofuran (THF) as the base/solvent combination, methyl 5-bromovalerate afforded only the ester exchange product, $Br(CH_2)_4COO(CH_2)_5OCH_2CH_3$ (**4a**), in 63% yield. Use of *n*-butyllithium altered neither the yield nor the reaction pathway, although slightly more starting material was recovered in the latter case.

An attempt was then made to block ester exchange and to enhance the possibility of $S_N2$ substitution by using *tert*-butyl 5-iodovalerate as substrate. In this case, a 32% yield of ester exchange product was isolated along with 14% of starting material, but no 5-substitution product could be detected. The iodide leaving group did prove

$$CH_3CH_2O(CH_2)_5O(CH_2)_4COOC(CH_3)_3$$
$$\not\nearrow$$
$$I(CH_2)_4COOC(CH_3)_3 + CH_3CH_2O(CH_2)_5OH$$
$$\searrow$$
$$I(CH_2)_4COO(CH_2)_5OCH_2CH_3 + CH_2{=}CHCH_2CH_2COO(CH_2)_5OCH_2CH_3$$

more prone to elimination than the other halogens. In both cases studied, a significant amount of $CH_2{=}CHCH_2CH_2COO(CH_2)_5OEt$, **5**, was isolated. Thus, the isolated yields of ester exchange product for the reactions of **3b** and **3c** were 43% and 54%, respectively. An attempt at direct substitution using the free bromo acid salt failed. The reactions attempted are illustrated in Table II. The product numbers refer to the reaction:

$$CH_3CH_2O(CH_2)_5OH\ (2) + X(CH_2)_4CO_2R\ (\mathbf{3a\text{–}d}) \rightarrow X(CH_2)_4CO_2(CH_2)_5OEt\ (\mathbf{4a,b}) + CH_2{=}CHCH_2CH_2CO_2(CH_2)_5OEt\ (5)$$

Why we have had no success in displacing a halide from the 5-position using an oxygen nucleophile when examples of other displacements abound is an interesting question. All but one of the nucleophiles shown in Table I are soft in the Pearson HSAB sense. Of the nucleophiles shown, only phenoxide is hard although its electron cloud is clearly more polarizable than would be a simple alkoxide. Alkyl halides are likewise generally regarded as soft electrophiles and the reactivity apparent in the table corresponds to this assessment. Of the examples shown, perhaps the most surprising is that between $CH_3OCOCH^-SO_2Ph$ and $Br(CH_2)_4COOCH_2CCl_3$.[9,10] In this case, the trichloroethoxide anion should be a reasonably good leaving group, and some addition to the carbonyl group might be expected. Of course, the nucleophile is relatively bulky, and this fact may account as much for the regioselectivity as does the nucleophile's softness.

(2) Gottlinger, H. G.; Sodroski, J. G.; Haseltine, W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 5781.
(3) Heuckeroth, R. O.; Glaser, L.; Gordon, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 8795.
(4) Heuckeroth, R. O.; Jackson-Machelski, E.; Adams, S. P.; Huhn, M.; Katoh, A.; Lu, T.; Gokel, G.; Gordon, J. I. *J. Lipid Biochem.* **1990**, *31*, 1121–1129.
(5) Heuckeroth, R. O.; Gordon, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 5262.
(6) Mussatto, M. C.; Savoia, D.; Trombini, C.; Urrani Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 260.
(7) Kissing, W.; Witkop, B. *Chem. Ber.* **1975**, *108*, 1623.
(8) Brown, E.; Dhal, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2190.
(9) Trost, B. M.; Verhoeven, T. R. *Tetrahedron Lett.* **1978**, *26*, 2275.
(10) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
(11) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *27*, 1461.
(12) Lavielle, S.; Bory, S.; Moreau, B.; Luche, M. J.; Marquet, A. *J. Am. Chem. Soc.* **1978**, *100*, 1558.
(13) Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137.
(14) Berkowitz, W. F.; Grenetz, S. C. *J. Org. Chem.* **1976**, *41*, 10.
(15) McIntosh, J. M.; Acquaah, S. D. *Can. J. Chem.* **1988**, *66*, 1752.
(16) Thomas, R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del, G. J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182.
(17) Taits, S. Z.; Dudinov, A. A.; Alashev, F. A.; Gol'dfarb, Yu. L. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1974**, 148.
(18) Kotva, R.; Cerny, A.; Semonsky, M. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1438.
(19) Ogawa, N.; Yoshida, T.; Aratani, T.; Koshinaka, E.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1988**, *36*, 2955.

Table II. Attempted Syntheses of 6,12-Dioxamyristic Acid Esters

| compd no. | solvent | X | R | base used | % recovered 2[a] | % recovered 3[b] | product no. | yield,[a] % |
|---|---|---|---|---|---|---|---|---|
| 3a | THF | Br | Me | NaH | 19 | 9 | 4a | 63 |
| 3a | THF | Br | Me | BuLi | 29 | 15 | 4a | 66 |
| 3a | THF | Br | Me | NaH[c] | 60 | 6 | 4a | 16 |
| 3a | DMF | Br | Me | NaH | 61 | 3 | 4a | 20 |
| 3b | THF | I | Me | NaH | 34 | 9 | 4b | 33 (10)[b,d] |
| 3c | THF | I | t-Bu | NaH | 14 | trace | 4b | 32 (22)[b,d] |
| 3d | THF | Br | H | NaH | 81 | 31 | | 0 |

[a] Isolated yield. [b] Determined by $^1H$ NMR. [c] An equimolar amount of 18-crown-6 was used. [d] The yield of $CH_2{=}CH(CH_2)_2CO_2(CH_2)_5OCH_2CH_3$ (5) is in parentheses.

**Aggregation State of the Intermediate Complex.** The reaction pathway (attack at carbon 1 or 5) may be controlled by the aggregation state of the nucleophile. If the nucleophile and substrate are coordinated, attack at the carbonyl may be favored sterically, especially if the ester adopts an extended conformation. In principle, a purely aliphatic alcohol would not coordinate in the bidentate fashion possible for an alkoxy alcohol.

When the analogous reaction of 1-iodopentane with 5-ethoxypentanol was attempted only 20% of 3,9-dioxatetradecane (10) was isolated. Clearly coordination of the carboxyl or ester function is not the only factor, although it may be playing a significant role. The converse of this experiment is to treat the halo ester with octanol. The latter is the same chain length as 5-ethoxypentanol but lacks the second coordinating site. The reaction and the results are shown below.

$$I(CH_2)_4COOCH_3 + CH_3(CH_2)_7O^- \rightarrow I(CH_2)_4COO(CH_2)_7CH_3\ (7,\ 23\%) + CH_2{=}CHCH_2CH_2COO(CH_2)_7CH_3\ (8,\ 27\%) + CH_3(CH_2)_7O(CH_2)_4COOCH_3\ (9,\ 3\%)$$

**Halo Acids and Halo Esters.** Although a combination of factors might account for the final result in this case, we thought it possible that the phenomenon is general. A number of halo acid or halo ester substrates are known to undergo nucleophilic substitution. The reactions of $\alpha$-halo acetic acid derivatives are especially well known. An on-line computer search of *Chemical Abstracts* showed that there are numerous recent examples of the general reaction

$$ROH + X(CH_2)_nCOOR' \rightarrow RO(CH_2)_nCOOR'$$

One or more recent examples were found for the cases in which $n$ = 1, 2, 3, 5, and 6. Somewhat older work was found in which 4-oxadodecanoic, -pentadecanoic, -hexadecanoic, and -octadecanoic acid derivatives were prepared.[20] The notable exception in this group is clearly the valerate esters.

**Conformational Effect.** The unusual behavior of the halo valerate ester system may be due to a conformational effect related to chelation or ion pairing. We have already shown that the poor yields in our attempted alkylation reaction are not due exclusively to an extended conformation of the halo ester. An examination of Dreiding molecular models suggested that there was nothing unusual about the molecule's extended conformation. It appeared to us, however, that the ester might adopt a chairlike conformation due to the organizing effect of sodium cation. It appears from the models that the ester and the halide are likely both to be equatorial.

Backside attack of the nucleophile on the halide is extremely hindered and the most accessible electrophilic site in this conformation is the $sp^2$ carbon. Of course, carbon nucleophiles seem to find the halide-bearing-carbon so aggregation may also be an accomplice in determining the fate of this system.

An experimental test of this conformational hypothesis was devised which also permitted examination of the role played by the chelating cation. We reasoned that use of a noncoordinating cation would favor halide displacement over olefin formation. We therefore attempted the phase transfer catalytic[21] Williamson ether synthesis[22] as shown in the equations below.

$$HO(CH_2)_6OH + DHP \rightarrow HO(CH_2)_6OTHP\ (38\%)$$

$$HO(CH_2)_6OTHP + Br(CH_2)_4COOC(CH_3)_3 \rightarrow THPO(CH_2)_6O(CH_2)_4COOC(CH_3)_3\ (32\%)$$

Since the tetrabutylammonium cation is too hindered for coordination of the type described above to be feasible, $S_N2$ attack at halogen rather than addition to the $sp^2$ carbonyl group should be favored. 1,6-Hexanediol was converted to its monotetrahydropyranyl (THP) derivative (11), and the monoprotected alcohol was then allowed to react with *tert*-butyl 5-bromovalerate in a two-phase mixture of 50% aqueous NaOH and toluene (4 h, ambient temperature, 10 mol % $Bu_4HSO_4$). After workup and chromatography over silica gel, 46% of unreacted starting material was reclaimed and the 5-substituted *tert*-butyl ester (12) was isolated in 32% yield. Based on unrecovered halo ester, the conversion was 75%. No olefinic or ester exchange products were isolated.

The dramatic increase in yield and the clear preference for "normal" substitution under phase-transfer conditions supports the chelation/chair conformation hypothesis posited above. Of course, the solvents differ in these experiments as well as the cations, but we believe that latter's influence controls the reaction course.

**Synthesis of 6,12-Dioxamyristic Acid.** The synthesis of this compound was ultimately accomplished as follows. 1,5-Pentanediol was monoethylated (1 equiv of $CH_3CH_2I$, NaH, THF, product: 2, 71%). The diol was also converted into its monotetrahydropyranyl ether (DHP, TsOH, $CH_2Cl_2$, 14, 54%).[23] Ethoxy alcohol 2 was tosylated (pyridine, TsCl, 0 °C) in 40% yield to afford oily 13. The low yield reflects the need to distill this reactive ether. Tosylate 13 was then allowed to react with mono-THP alcohol 14 (NaH, THF, reflux, 24 h) to afford, after deprotection,[24] the diether alcohol, 16, in 37% yield. Oxidation using Kiliani reagent ($Na_2Cr_2O_7{\cdot}2H_2O/H_2SO_4/H_2SO_4/H_2O$)[25] afforded previously unknown 6,12-dioxa-

(20) Mayer, B.; Asselineau, J. *Compt. Rend. Ser. C* **1966**, *262*, 668.

(21) (a) Weber, W. P.; Gokel, G. W. *Phase Transfer Catalysis in Organic Synthesis*; Springer Verlag: Berlin, 1977. (b) Starks, C. M.; Liotta, C. L. *Phase Transfer Catalysis*; Academic Press: New York, 1978.

(22) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, 3251.

(23) Ngooi, T. K.; Scilimati, A.; Guo, Z.-W.; Sih, C. J. *J. Org. Chem.* **1989**, *54*, 911.

(24) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.

tetradecanoic acid, 1, in 52% yield as a colorless oil.

$$HO(CH_2)_5OH \rightarrow CH_3CH_2O(CH_2)_5OH \quad (2)$$

$$CH_3CH_2O(CH_2)_5OH + TsCl \rightarrow CH_3CH_2O(CH_2)_5OTs \quad (13)$$

$$HO(CH_2)_5OH + DHP \rightarrow THP\text{-}O(CH_2)_5OH \quad (14)$$

$$THPO(CH_2)_5OH + CH_3CH_2O(CH_2)_5OTs \rightarrow CH_3CH_2O(CH_2)_5O(CH_2)_5OTHP \quad (15)$$

$$CH_3CH_2O(CH_2)_5O(CH_2)_5OTHP \rightarrow CH_3CH_2O(CH_2)_5O(CH_2)_5OH \quad (16)$$

$$CH_3CH_2O(CH_2)_5O(CH_2)_5OH \rightarrow CH_3CH_2O(CH_2)_5O(CH_2)_4COOH \quad (1)$$

## Summary and Conclusion

The synthesis described above, although producing an interesting and hitherto unknown compound, is unremarkable from both tactical and strategic perspectives. It is interesting, however, that the more obvious approaches failed. The 5-halovalerate esters appear to be an unusual group of substrates when metal alkoxides are used as nucleophiles. It appears that the hardness of the nucleophile, the aggregation state of the intermediate complex, and the molecular conformation all contribute to these unusual results. Of these, the chelation-induced conformation appears to be the most important factor. Using phase-transfer catalysis permits the halovalerate esters to react in an extended conformation and substitution results are more normal.

## Experimental Section

$^1H$ NMR were recorded in $CDCl_3$ (unless otherwise noted) at 60, 300, or 400 MHz. High-resolution mass spectra were obtained by using a Cs incident beam at 25 keV and a nitrobenzyl alcohol/LiI matrix. Peak matching was done on CsI. Column chromatography was carried out with EM Science $Al_2O_3$ (80–230 mesh) and Merck Kieselgel 60 (70–230 mesh). Precoated sheets (aluminum oxide $60F_{254}$ neutral Type E or silica gel $60F_{254}$, 0.2 mm thick) were used for TLC analysis. Combustion analyses were conducted by Atlantic Microlab. Inc. Atlanta, GA.

**5-Ethoxypentan-1-ol (2).** NaH (4.2 g, 0.11 mol, hexane-washed) was suspended in dry THF (400 mL) and added to pentane-1,5-diol (10.4 g, 0.1 mol) in THF (50 mL), the mixture was stirred for 1 h at room temperature, $CH_3CH_2I$ (17.2 g, 0.11 mol) in THF (50 mL) was added, and the resultant mixture was refluxed for 48 h. The solvent was evaporated, and the residue was dissolved in EtOAc (300 mL), washed with $H_2O$ (2 × 50 mL), brine (50 mL), and dried ($Na_2SO_4$). The residue was purified by column chromatography on alumina (10% 2-PrOH–hexane) and then distilled (Kugelrohr) to give the product (**2**, 9.4 g, 71%): bp 45–46 °C (0.005 Torr); IR (neat) 3400 (br) and 1115 $cm^{-1}$; $^1H$ NMR 1.22 (t, 3 H, $J$ = 6.8 Hz), 1.42 (m, 2 H), 1.56 (m, 4 H), 3.43 (t, 4 H, $J$ = 5.8 Hz), 3.48 (q, 2 H, $J$ = 6.8 Hz), and 3.58 ppm (br s, 1 H).

**General Procedure for the Reaction of 5-Ethoxypentan-1-ol with Alkyl 5-Halovalerates.** The reaction of 5-ethoxypentan-1-ol (0.8 g, 6 mmol) and alkyl 5-halovalerates (**3a–c**, 6 mmol) in the presence of NaH (0.25 g, 6.3 mmol) in dry THF (50 mL) was carried out as described above. The solvent was evaporated, and the residue was dissolved in AcOEt (120 mL), washed with $H_2O$ (2 × 50 mL) and brine (50 mL), and dried ($Na_2SO_4$). The crude product was chromatographed on silica gel with AcOEt–hexane (1:1) and distilled (Kugelrohr).

**Reaction of 3a.** The reaction with 5-bromovalerate (**3a**) under the conditions described above gave ethoxypentyl 5-bromovalerate (**4a**): Kugelrohr oven temperature 102–104 °C (0.2 Torr); IR (neat) 1750 $cm^{-1}$; $^1H$ NMR 1.15 (t, 3 H, $J$ = 7 Hz), 1.4–1.9 (m, 10 H), 2.28 (t, 2 H, $J$ = 6 Hz), 3.35 (t, 4 H, $J$ = 6.5 Hz), 3.42 (q, 2 H, $J$ = 7 Hz), and 4.0 ppm (t, 2 H, $J$ = 6.5 Hz). Anal. Calcd for $C_{12}H_{23}BrO_3$: C, 48.82; H, 7.85. Found: C, 49.51; H, 7.91.

**Reaction of 3b.** The reaction of methyl 5-iodovalerate (**3b**) as described above gave a mixture of ethoxypentyl 5-iodovalerate (**4b**, 0.68 g, 33%) and ethoxypentyl 4-pentenoate (**5**, 0.13 g, 10%) in a 75:25 ratio (determined by $^1H$ NMR) which could not be separated by column chromatography and/or Kugelrohr distillation: $^1H$ NMR 1.20 (t, 3 H), 1.4–1.9 (m, 9.5 H), 2.2–2.5 (m, 2 H), 3.17 (t, 1.5 H, $J$ = 6 Hz), 3.2–3.6 (m, 4 H), 4.05 (t, 2 H, $J$ = 2 Hz), 4.8–5.2 (m, 0.5 H), and 5.5–5.9 ppm (m, 0.25 H).

**Reaction of 3c.** The reaction of *tert*-butyl 5-iodovalerate (**3c**) under the conditions described above gave the same mixture of compounds **4b** (0.66 g, 32%) and **5** (0.29 g, 22%) in a 60:40 ratio, again determined by NMR.

**Attempted Reaction of Octan-1-ol with Methyl 5-Iodovalerate: Formation of 7, 8, and 9.** This reaction was conducted as described above. Column chromatography [silica gel with EtOAc–hexane (1:5)] gave two major fractions. The first fraction was a 40:60 mixture of octyl 5-iodovalerate (**7**, 0.37 g, 18%) and octyl 4-pentenoate (**8**, 0.34 g, 27%): $^1H$ NME 0.90 (t, 3 H, $J$ = 6 Hz), 1.1–1.9 (m, 14.8 H), 2.2–2.5 (m, 2 H), 3.18 (t, 0.8 H), 4.07 (t, 2 H, $J$ = 6 Hz), 4.8–5.2 (m, 1.2 H), and 5.5–5.8 ppm (m, 0.6 H). The second fraction was a 60:40 mixture of **7** (0.10 g, 5%) and methyl 6-oxatetradecanoate (**9**, 0.045 g, 3%): $^1H$ NMR 0.89 (t, 3 H, $J$ = 6 Hz), 1.2–1.9 (m, 16 H), 2.2–2.5 (m, 2 H), 3.18 (m, 1.2 H), 3.2–3.5 (m, 1.6 H), 3.67 (s, 1.2 H), and 4.04 ppm (t, 1.2 H, $J$ = 6 Hz).

**Attempted Reaction of 5-Ethoxypentan-1-ol with Iodopentane: Formation of 3,9-Dioxatetradecane (10).** The title reaction was conducted as described above, affording 3,9-dioxatetradecane (**10**, 0.24 g, 20%) as the product: Kugelrohr oven temperature 42–46°C (0.13 Torr); $^1H$ NMR 0.91 (t, 3 H, $J$ = 6 Hz), 1.22 (t, 3 H, $J$ = 7 Hz), 1.2–1.7 (m, 12 H), 3.38 (t, 6 H, $J$ = 7 Hz), and 3.45 ppm (q, 2 H, $J$ = 7 Hz). Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 71.32; H, 12.90.

**6-(Tetrahydropyranyloxy)hexan-1-ol (11).** To an ice-cooled solution of 1,6-hexandiol (5.0 g, 0.042 mol) in dry $CH_2Cl_2$ (40 mL) containing *p*-TsOH (0.8 g, 0.004 mol) was added dropwise a solution of dihydropyran (4.25 mL, 0.046 mol) in $CH_2Cl_2$ (10 mL) during 1 h. The reaction mixture was stirred for 1.5 h at 0 °C and at ambient temperature for 30 min, $NaHCO_3$ (0.5 g) and $H_2O$ (15 mL) were added, and the organic phase was washed ($H_2O$, 3 × 15 mL), dried ($Na_2SO_4$), and concentrated in vacuo to give a colorless oil which was purified by flash chromatography using 30% ethyl acetate in hexane containing 0.2% $Et_3N$ as eluent to give **11** (3.3 g, 38%) as a thick, colorless oil: $R_f$ 0.26 (50% EtOAc/hexane); $^1H$ NMR 1.3–1.9 (m, 14 H), 2.25 (br s, 1 H), 3.3–3.8 (m, 6 H), 4.57 (m, 1 H); FAB mass spectrum, $m/e$ 209 (M + Li); high-resolution FAB mass spectrum, $m/e$ 209 (M + Li); high-resolution FAB mass spectrum, $m/e$ calculated for $C_{11}H_{22}O_3Li$ 209.1729, found 209.1754.

**Reaction of 11 with *tert*-Butyl 5-Bromovalerate To Form *tert*-Butyl 6-Oxa-12-(2-tetrahydropyranyloxy)dodecanoate (12).** To an ice-cold solution of **11** (0.7 g, 0.0035 mol) and *tert*-butyl 5-bromovalerate (0.6 g, 0.0029 mol) in toluene (2 mL) were added 50% aqueous NaOH solution (1.4 mL) and $Bu_4HSO_4$ (0.12 g, 0.35 mmol), and the mixture was stirred for 30 min at 0 °C and then for 4 h at ambient temperature, poured into 10 mL of ice–water, and extracted with EtOAc (2 × 15 mL). The organic phase was washed with water (3 × 15 mL), dried over $Na_2SO_4$ (excess), and concentrated in vacuo to afford a pale, yellow liquid (1.1 g), which was further purified by flash chromatography using 20% EtOAc in hexane containing 0.2% $Et_3N$ as the eluent. The unreacted bromovalerate (0.31 g, 46%) eluted first, followed by *tert*-butyl 6-oxa-12-(2-tetrahydropyranyloxy)dodecanoate, **12**. The fractions containing **12** were combined, concentrated, and dried under high vacuum to afford pure **12** (0.34 g, 32%) as a colorless oil: $R_f$ 0.63 (50% EtOAc in hexane); $^1H$ NMR 1.3–1.9 (m, 27 H), 2.24 (t, 2 H, $J$ = 6 Hz), 3.39 (m, 5 H), 3.75 (m, 1 H), 3.87 (m, 1 H), 4.56 (t, 1 H, $J$ = 6 Hz); FAB mass spectrum, $m/e$ 376 (M + $NH_4$); high-resolution FAB mass spectrum, calculated for $C_{20}H_{38}O_5Li$ 365.2879, Found 365.2901.

**Synthesis of 6,12-Dioxamyristic Acid. 6-Oxaoctyl *p*-Toluenesulfonate (13).** Compound **2** (3.3 g, 0.025 mol) was dissolved in pyridine (25 mL) and then cooled to 0 °C. To a mixture was added *p*-TsCl (5.7 g, 0.03 mol) with vigorous stirring

(25) Kiliani, H.; Merk, B. *Chem. Ber.* **1901**, *34*, 3562.

for 2 h, the mixture was then stirred at room temperature for 5 h, poured onto ice, and extracted with EtOAc (150 mL), and the organic phase was washed with water (50 mL), brine (50 mL), and dried ($Na_2SO_4$). The residual oil was purified by Kugelrohr distillation, 128-134 °C (0.08 Torr), to give the product (13, 3 g, 40%): IR (neat) 1355 and 1180 $cm^{-1}$; $^1H$ NMR 1.17 (t, 3 H, $J$ = 7 Hz), 1.3-1.8 (m, 6 H), 2.43 (s, 3 H), 3.36 (t, 2 H, $J$ = 7 Hz), 3.42 (q, 2 H, $J$ = 7 Hz), 4.0 (t, 2 H, $J$ = 6 Hz), 7.28 (d, 2 H, $J$ = 8 Hz), and 7.76 ppm (d, 2 H, $J$ = 8 Hz).

**5-(Tetrahydropyranyloxy)pentan-1-ol (14).** To a mixture of pentane-1,5-diol (5.2 g, 0.05 mol) and *p*-TsOH (0.1 g, 0.53 mmol) in $CH_2Cl_2$ (120 mL) was added slowly dihydropyran (4.6 g, 0.055 mol) in $CH_2Cl_2$ (30 mL) at 0 °C. After the mixture was stirred for 2 h at 0 °C and 1 h at room temperature, saturated $NaHCO_3$ (50 mL) was added to the reaction mixture. The $CH_2Cl_2$ layer was washed with saturated $NaHCO_3$ (50 mL) and water (50 mL) and dried ($MgSO_4$). The residue was purified by column chromatography on silica gel with EtOAc-hexane (1:1,v/v) and Kugelrohr distillation at 80-85 °C (0.1 Torr) to give the product (14, 5.1 g, 54%): IR (neat) 3450 (br) and 1135 $cm^{-1}$; $^1H$ NMR 1.3-1.9 (m, 12 H), 2.4 (br s, 1 H), 3.3-3.9 (m, 6 H), and 4.58 ppm (m, 1 H).

**6,12-Dioxatetradecan-1-ol (16).** The reaction of compound 13 (2.86 g, 0.01 mol) and compound 14 (1.88 g, 0.01 mol) in the presence of NaH (0.4 g, 0.011 mol) in dry THF (70 mL) was carried out in the same manner as described above. The crude oil was chromatographed on silica gel to give a mixture (2.4 g) of the starting material (13) and compound 15 (40:60). To this mixture in MeOH (50 mL) was added *p*-TsOH (28 mg), and the reaction mixture was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was dissolved in EtOAc (150 mL). The organic phase was washed with 5% $NaHCO_3$ (2 × 50 mL), water (50 mL), and brine (50 mL) and dried ($Na_2SO_4$). The residue was purified by column chromatography on silica gel with EtOAc-hexane (1:1) and Kugelrohr distillation at bp 88-92 °C (0.05 Torr) to give the product (16, 0.8 g, total yield 37%): IR (neat) 3460 (br) and 1115 $cm^{-1}$; $^1H$ NMR 1.18 (t, 3 H, $J$ = 7 Hz), 1.3-1.8 (m, 12 H), 2.1 (br s, 1 H), 3.38 (t, 8 H, $J$ = 6.5 Hz), and 3.43 ppm (q, 2 H, $J$ = 7 Hz).

**6,12-Dioxatetradecanoic Acid (1).** Kiliani reagent[25] was prepared in situ by dissolving $Na_2Cr_2O_7 \cdot 2H_2O$ (3 g) in a cold solution of $H_2SO_4$ (4 g) and water (13.5 g). To a solution of compound 16 (1.2 g, 5.5 mmol) in AcOH (28 mL) was added Kiliani reagent (20 g) at 0 °C. The reaction mixture was stirred for 7 h at room temperature. Water (120 mL) was added to the mixture and then extracted with EtOAc (2 × 100 mL). The organic phase was washed with water (2 × 30 mL) and dried ($Na_2SO_4$). The residual oil was purified by column chromatography on silica gel with $CHCl_3$-MeOH (7:1) and subsequent Kugelrohr distillation at bp 128-132 °C (0.1 Torr) to give the product (1) (0.7 g, 52%): IR (neat) 3000 (br) and 1730 $cm^{-1}$; $^1H$ NMR 1.23 (t, 3 H, $J$ = 7.4 Hz), 1.3-1.8 (m, 10 H), 2.38 (t, 2 H, $J$ = 5.4 Hz), 3.3-3.6 (m, 8 H), and 9.98 ppm (br s, 1 H). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 61.95; H, 10.43%.

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**Supplementary Material Available:** NMR spectra of relevant compounds (11 pages). Ordering information is given on any current masthead page.

# Nazarov Reaction of Trisubstituted Dienones: Mechanism Involving Wagner-Meerwein Shift

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The Nazarov reactions of trisubstituted $\alpha,\alpha'$-dienones were studied. Whereas $\alpha,\beta$-dimethyl-$\beta'$-alkyl $\alpha,\alpha'$-dienones gave 2,3-dimethyl-4-alkyl-2-cyclopentenones when heated in concentrated sulfuric acid, the reaction of $\beta,\beta$-dimethyl-$\beta'$-alkyl $\alpha,\alpha'$-dienones afforded 3,4-dimethyl-4-alkyl-2-cyclopentenones as the rearranged products. A mechanistic investigation using two deuterated dienones suggests that the Nazarov reactions of the latter dienones are accompanied by Wagner-Meerwein shifts to form the most stable carbocations.

There have been many investigations on the Nazarov reaction[1,2] from mechanistic and synthetic viewpoints. The original Nazarov reaction is the ring closure of $\alpha,\alpha'$-dienones (divinyl ketones) or $\alpha,\beta'$-dienones (allyl vinyl ketones) in strongly acidic media. This reaction proceeds via conrotatory $4\pi$ electronic cyclization of pentadienyl cations[3] and provides an efficient route to 2-cyclopentenones, useful intermediates for organic synthesis.[4] Among the many studies of this reaction, a few examples of abnormal Nazarov reactions with rearrangements were found in substituted dienones.[5] These are considered to occur by rearrangement of the cyclopentenyl cations formed by a normal electronic cyclization of the $4\pi$ system to the most stable cyclopentenyl cations, which give the final products. These competing rearrangements are often regarded as a shortcoming of the Nazarov reaction but are suggestive,

(1) Nazarov, I. N.; Zaretskaya, I. I.; Sorkia, T. I. *Zh. Obshch. Khim.* **1960**, *30*, 746; *Chem. Abstr.* **1961**, *55*, 524h. Nazarov, I. N.; Zaretskaya, I. I. *Zh. Obshch. Khim.* **1957**, *27*, 693. For a recent review, see: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.

(2) Recent papers for the Nazarov reaction, see: (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696. (c) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *Ibid.* **1980**, *45*, 395. (d) Shoppee, C. W.; Cooke, B. J. *J. Chem. Soc., Perkin Trans. I* **1972**, 2271.

(3) Shoppee, C. W.; Cooke, B. J. *J. Chem. Soc., Perkin Trans. I* **1973**, 1026.

(4) For a review on the synthesis of 2-cyclopentenones, see: (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Ellison, R. A. *Synthesis* **1973**, 397.

(5) (a) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017. (b) Hirano, S.; Takagi, S.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 169. (c) Hirano, S.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1974**, 1429.

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