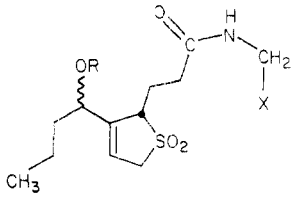
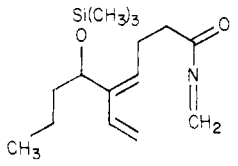
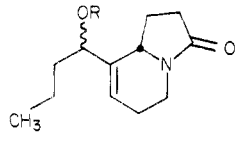
various bases.[9] However, base deprotonation occurred very readily in the dihydrothiophene dioxide ring, and a number of C-alkylation products were detected. Alternatively, amide **7** was combined with chloromethyl methyl sulfide in TFA[10] to give the (thiomethyl)amide **8** (62%; IR (film) 3450, 1680 cm^{-1}; NMR ($CDCl_3$) δ 4.3 (2 H, d), 2.2 (3 H, s)). Reduction of **8** with sodium borohydride/$CeCl_3$ in methanol (room temperature, 5 min) gave the allylic alcohol **9** as a mixture of diastereomers (90%; IR (film)





9, X = SCH_3; R = H
10, X = OAc; R = H
11, X = OAc; R = $Si(CH_3)_3$

12

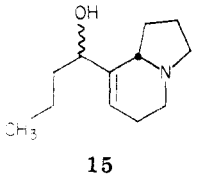


13, R = $Si(CH_3)_3$
14, R = H

3400, 1660 cm^{-1}).[11] The thiomethyl group of **9** could be smoothly exchanged with mercuric acetate in glacial acetic acid to afford acetate **10** (82%; IR (film) 3300, 1740, 1680 cm^{-1}). The alcohol functionality of **10** was silylated (Me_3SiCl, pyridine, hexamethyldisilazane) to give **11** which was used without purification.

A dilute toluene solution of **11** was slowly passed through a 15-cm column of glass helices maintained at 370–390 °C, providing bicyclic lactam **13** in 68% yield as a mixture of diastereomers (IR (film) 1680 cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, m), 4.3 (3 H, m)). This cyclization probably occurs via the unisolable diene–acylimine **12**.[9,12]

Hydrolysis of the silyl-protecting group of **13** (methanol/H_2O/HCl) led to alcohol **14** (IR (film) 3400, 1680 cm^{-1}) which upon reduction with a solution of Dibal-H in THF gave amino alcohol **15** (91%).[13] Oxidation of the allylic



15

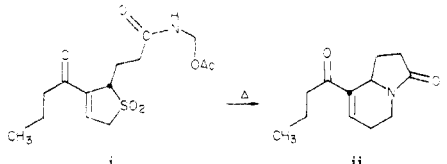
alcohol group of **15** with Me_2SO/trifluoroacetic anhydride (CH_2Cl_2, −78 °C) gave racemic elaeokanine A (62%) having IR, ^1H NMR, UV, and mass spectra identical with those of natural material.[14]

We expect that the approach outlined above can be used for the synthesis of many different *Elaeocarpus* alkaloids. Also, we are currently applying the intramolecular imino Diels–Alder reaction to preparation of several other classes of alkaloids.

Acknowledgment. We are grateful to the National Cancer Institute for support of this work (CA 25145), to Dr. R. Minard for mass spectra, and to A. Freyer for FT NMR spectra.

Registry No. (±)-**1**, 73971-21-8; **2**, 65921-74-6; *E*-**3**, 73971-22-9; *Z*-**3**, 73971-23-0; (±)-**4**, 73971-24-1; **5**, 73971-25-2; (±)-**6**, 73971-26-3; (±)-**7**, 73971-27-4; (±)-**8**, 73971-28-5; (±)-**9** (isomer 1), 73971-29-6; (±)-**9** (isomer 2), 73971-30-9; **10**, 73971-31-0; **11**, 73971-32-1; (±)-**13** (isomer 1), 73971-33-2; (±)-**13** (isomer 2), 73971-34-3; **14**, 73971-35-4; **15**, 33023-02-8; 4-pentenal, 2100-17-6; mercaptoacetaldehyde, 4124-63-4; chloromethyl methyl sulfide, 2373-51-5.

(9) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073.
(10) Bernardi, L.; DeCastiglione, R.; Scarponi, U. *J. Chem. Soc., Chem. Commun.* **1975**, 320.
(11) Luche, J. L.; Rodriques-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.
(12) Direct pyrolysis of i, prepared by treatment of **8** with $Hg(OAc)_2$/HOAc, did produce some ii, but the yield was generally poor and the cyclization route via **11** was preferable. Pyrolysis of alcohol **10** gave **14** in low yield.



i ii

(13) Elaeokanine B has been found to have the planar structure shown in **15**.[2] However, the stereochemistry of this alkaloid has not been established.
(14) We are indebted to Dr. J. A. Lamberton for providing copies of the IR, UV, and NMR spectra of natural elaeokanine A. Dr. Lamberton has informed us that an authentic sample of this alkaloid is unfortunately no longer available.
(15) A. P. Sloan Foundation Fellow, 1975–1979; Recipient of a NIH Research Career Development Award, 1975–1980 (HL-00541).

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Thallium in Organic Synthesis. 56. A Novel Oxidative Intramolecular Cyclization/Rearrangement of 5-Norbornene-*trans*-2,3-dicarboxylic Acid with Thallium(III) Trifluoroacetate (TTFA)

Summary: Treatment of 5-norbornene-*trans*-2,3-dicarboxylic acid (**5**) with thallium(III) trifluoroacetate (TTFA) and BF_3·Et_2O results in oxidative intramolecular cyclization, accompanied by rearrangement, to give the previously unknown 5,7-dihydroxy-2,3-norbornanedicarboxylic acid di-γ-lactone (**9**).

Sir: The reaction of thallium(III) acetate (TTA) and other electrophiles with norbornene mono- and dicarboxylic acids and various derivatives to form norbornane lactones is well-documented.[1-3] The products obtained from TTA-induced oxidative lactonization are dependent upon the reaction conditions employed. At room temperature, it is possible to isolate, in high yield, the intermediates **2**, **4**, and **6** which result from oxythallation/lactonization,[2] whereas at elevated temperatures the initially formed organothallium compound, e.g., **2**, decomposes to the acetate **7** (Scheme I). The lactones **2**, **4**, and **6** may be stored at room temperature for several days and thus are among the

(1) (a) R. M. Moriarty and H. Gopal, *Tetrahedron Lett.*, 347 (1972); (b) R. M. Moriarty, H. Gopal, J. L. Flippen, and J. Karle, *ibid.*, 351 (1972).
(2) A. McKillop, M. E. Ford, and E. C. Taylor, *J. Org. Chem.*, **39**, 2434 (1974).
(3) S. Uemura, H. Miyoshi, M. Okano, I. Morishima, and T. Inubushi, *J. Organomet. Chem.*, **165**, 9 (1979).

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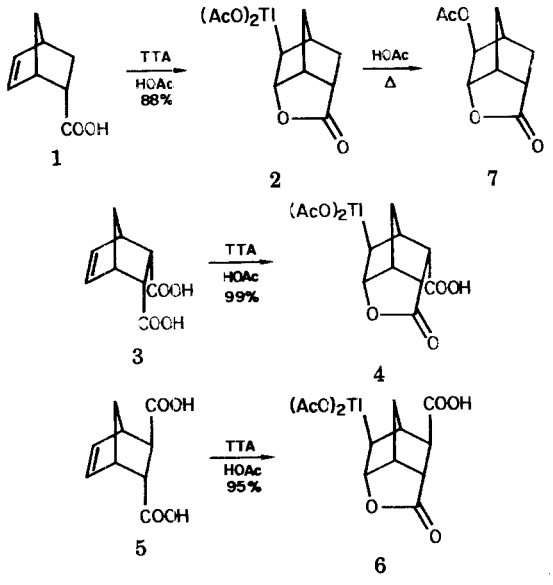
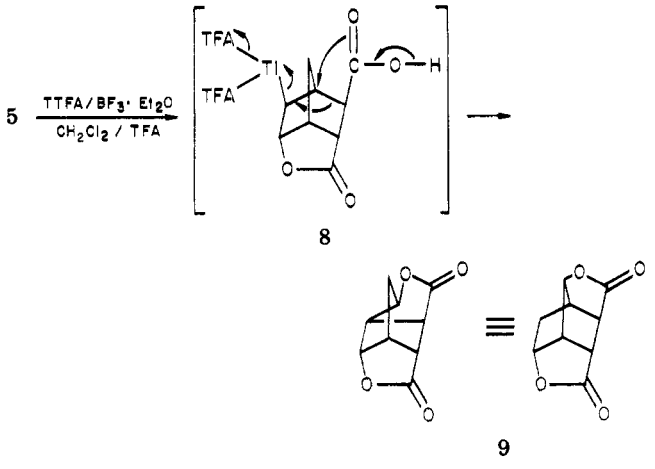
Scheme I



Scheme II



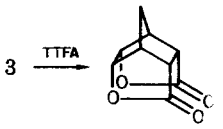
most stable oxythallation adducts known, few of which have been isolated.[2]

We report that the reaction of 5-norbornene-*trans*-2,3-dicarboxylic acid (**5**) with thallium(III) trifluoroacetate (TTFA) and BF_3·Et_2O in CH_2Cl_2/TFA does not yield a stable oxythallation adduct analogous to **6**. Instead, the previously unknown 5,7-dihydroxy-2,3-norbornanedicarboxylic acid di-γ-lactone **9** is isolated in 52% yield.[4] It is presumably formed by rearrangement of the unstable organothallium lactone **8** (Scheme II); the decreased stability of **8** compared with the TTA analogue **6** reflects the lower reduction potential imparted to Tl(III) by trifluoroacetate ligands.[5] Exclusion of BF_3·Et_2O from the reaction mixture lowers the yield to 25%.[6]

The procedure for the preparation of **9** is as follows. A mixture of 35 mL of CH_2Cl_2 and 3 mL of BF_3·Et_2O is added to a solution of 5.5 mmol (3.0 g) of TTFA in 12 mL of TFA. To this mixture is added a solution of 5.0 mmol (0.91 g) of **5**[7] in a minimum amount of CH_2Cl_2/TFA. The reaction mixture is stirred under N_2 at room temperature for 2.5 h, then cooled to 0 °C, and treated with 20 mL of *tert*-butyl alcohol and 50 mL of H_2O. The organic layer is separated and the aqueous layer extracted with a 50-mL portion of CH_2Cl_2. The combined organic layers are washed with 100 mL of water and two 75-mL portions of saturated aqueous sodium bicarbonate,[8] dried over Na_2SO_4, and evaporated to give 505 mg of nearly pure **9**, which is recrystallized from ethanol to afford 465 mg (52%) of pure **9**, mp 245–247 °C. Sublimation raises the melting point to 246–247.5 °C.

Evidence supporting the intermediacy of the oxythallation adduct **8** was obtained by treatment of **6** with TFA and BF_3·Et_2O at room temperature, which gave small and variable amounts (2–5%) of the dilactone **9**. Wagner–Meerwein shifts similar to that shown in Scheme II have been reported by Moriarty and Gopal;[1] in these cases the solvent, acetic acid, provides the carboxylate group which is captured in the course of the rearrangement. By contrast, no major product incorporating TFA is formed from **8**, presumably reflecting the poorer nucleophilicity of TFA.

5-Norbornene-*endo-cis*-2,3-dicarboxylic acid (**3**) reacts with various electrophiles to yield dilactone **10**. Treatment



10

of **3**[9] with TTFA/BF_3·Et_2O, as described for the oxidation of **5** (vide supra, with a 12-h reaction time), yields **10** (27%), mp 268–270 °C (lit. mp 274–275.5 °C,[10] 266 °C,[11] 264–266 °C,[12] 274–275 °C[13]). This product is identical in all respects with that obtained by lead tetraacetate oxidation of **3**.[10]

Extension of this reaction to include trans-substituted derivatives of **5** containing other nucleophilic functionalities (e.g., alcohols, amines, amides, thiols, olefins) should afford a variety of novel analogues of dilactone **9**. For example, reduction of **5** to the biscarbinol, followed by treatment with TTFA, smoothly affords the bisether **11**.[14] Further studies in this area are in progress.

(4) ^1H NMR ($CDCl_3$) δ 5.15 (br s, H-7), 4.90–5.10 (m, H-5), 3.70 (m, H-4), 3.10 (br s, H-2), 2.90 (m, H-1), 2.70 (d, H-3), 2.10–2.40 (octet, H-6a), 1.70–1.95 (d, H-6b); ^{13}C NMR ($CDCl_3$) 30.9 (C-6), 40.7 (C-1), 47.7, 47.9, 51.3 (C-2, C-3, C-4; order uncertain), 80.4 (C-5), 85.4 (C-7), 175.3, 175.5 ppm (C-8, C-9; order uncertain); m/e^+ 180. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.94; H, 4.45.

(5) A. McKillop and E. C. Taylor, *Adv. Organomet. Chem.*, 11, 147 (1973).

(6) Addition of BF_3·Et_2O often improves the yields of TTFA oxidation reactions, although its mechanistic role is not clear.

(7) Obtained by hydrolysis of the corresponding diacid chloride, which was prepared by the procedure of K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **514**, 197 (1934).

(8) The basic and aqueous washings were designed to remove acidic and water-soluble byproducts resulting from incomplete lactonization and adventitious solvolysis of the intermediate oxythallation adduct **8**. This complex mixture of byproducts was not investigated further.

(9) Obtained by hydrolysis of the corresponding anhydride, which was prepared by the procedure of O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).

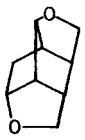
(10) G. I. Fray, R. J. Hilton, and J. M. Teire, *J. Chem. Soc. C*, 592 (1966).

(11) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **514**, 1 (1934).

(12) H. Kwart and L. Kaplan, *J. Am. Chem. Soc.*, **76**, 4078 (1954).

(13) A. Winston and P. Wilder, Jr., *J. Am. Chem. Soc.*, **76**, 3045 (1954).

(14) TTFA (1.2 g, 1 equiv) is added to a solution of 308 mg (2 mmol) of 5-norbornene-*trans*-2,3-dicarbinol in 100 mL of acetonitrile at room temperature (*no* BF_3). After a period of 60–72 h the mixture is diluted with 100 mL of methylene chloride, washed with water (3 × 100 mL), dried (Na_2SO_4), evaporated, and filtered through a short column containing a layer of Florisil over a layer of silica gel (5% acetone/chloroform) to yield 160 mg of crude product, shown by GC to contain 110 mg (36%) of the desired bisether **11**: NMR ($CDCl_3$) δ 3.60–4.50 (m, 6 H), 2.64–2.85 (m, 2 H), 2.10–2.36 (m, 3 H), 1.80–2.07 (m, 1 H); ^{13}C NMR ($CDCl_3$) 30.0, 30.4, 41.0, 42.5, 46.8, 54.1, 70.9, 77.7, 83.8 ppm; exact mass calcd for $C_9H_{12}O_2$ m/e 152.0837, found 152.0837.



11

Acknowledgment. We are indebted to the National Science Foundation (Grant No. CHE76 16506) for support of this work.

Registry No. 3, 3853-88-1; 3 anhydride, 2746-19-2; 5, 1200-88-0; 5 diacid chloride, 4582-21-2; 6, 51606-65-6; 8, 73971-18-3; 9, 73971-19-4; 10, 5826-27-7; 11, 73971-20-7; thallium(III) trifluoroacetate, 23586-53-0; 5-norbornene-*trans*-2,3-dicarbinol, 699-96-7.

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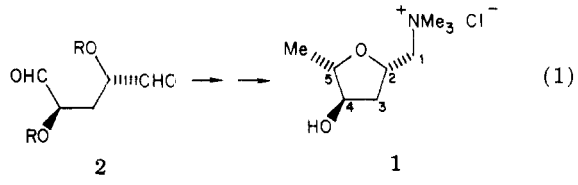
Chelation-Controlled Synthesis of (±)-Muscarine

Summary: The chelation-controlled addition of Grignard reagents to chiral α-alkoxy aldehydes to give threo diol derivatives is synthetically useful in highly oxygenated systems and is used here as the key step in a novel synthesis of (±)-muscarine from cyclopentadiene.

Sir: We recently reported that various organometallic reagents could be reacted with chiral α- and β-alkoxy aldehydes to give addition products with moderately high relative asymmetric induction.[1] In order to delineate the scope of this type of reaction and to illustrate its use, we have undertaken chelation-controlled syntheses of several naturally occurring materials of biological interest. One of these compounds is muscarine (1), the major cholinomimetic constituent of the poisonous mushroom *Amanita muscaria* or fly agaric.[2]

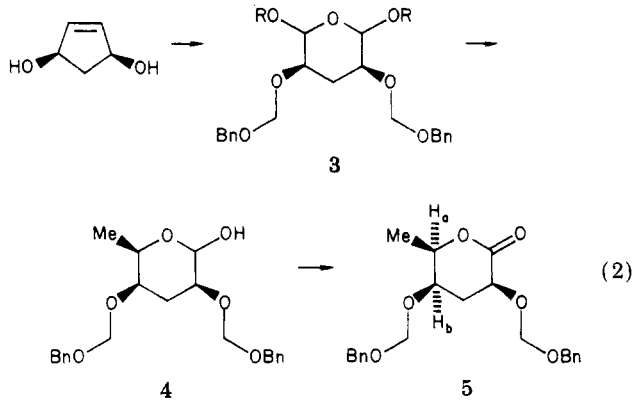
The central transformation in this synthesis is the stereoselective addition of a methyl nucleophile to the meso dialdehyde 2 (eq 1). On the basis of our previous work,



2 1 (1)

it was anticipated that the addition of a Grignard reagent would proceed via Cram's cyclic transition state[3] and yield the corresponding threo alcohol.[1] Internal etherification with inversion at C-5 would then produce a tetrahydrofuran having the connectivity and stereochemistry of 1.

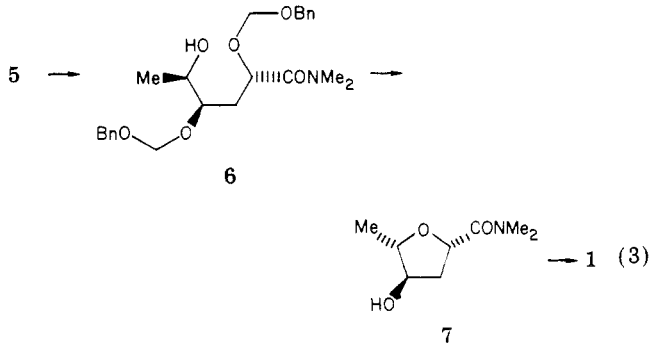
Our preparation of the required dialdehyde 2 (R = CH_2OBn) began with the singlet oxygenation product of cyclopentadiene[4] which was protected ($PhCH_2OCH_2Cl$, *i*-Pr_2NEt; 25 °C) and ozonized [(a) O_3, CH_2Cl_2, −78 °C; (b) Zn, HOAc, 0–25 °C]. The product of these operations turned out not to be 2 itself but the corresponding cyclic hydrate 3 (R = H) (eq 2). Interestingly, this compound



3 4 5 (2)

was not changed by treatment with methylmagnesium bromide under a variety of conditions. Since the lack of reactivity presumably derives from rapid conversion to the dialkoxide, the hydrate was converted to the corresponding diacetate (3, R = Ac) so that methyl Grignard addition might provide in situ generation[5] of 2 and subsequent chelation-controlled addition to one of the α-alkoxy aldehydes. Although the outcome of the desired Grignard reaction was strongly dependent on precise reaction conditions,[6] we were able to produce 4 reproducibly with (5–6):1 threo–erythro stereoselectivity by the addition of 3 (R = Ac) to excess methylmagnesium bromide in 2-methyltetrahydrofuran at −35 °C. The desired threo product (4) was readily separated[7] from the minor erythro isomer and a trace of the double-addition product by flash chromatography.[8] The overall isolated yield of pure 4 was 40% from the starting cyclopentenediol.[9]

Although the threo assignment was ultimately proven by conversion of 4 to muscarine, stereochemical support was provided at this stage by ^1H NMR examination of the derived lactone 5 ($CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2; 90% yield) and its C-5 epimer. These compounds displayed the expected values for $J_{a,b}$ of 3 and 9 Hz, respectively. Final conversion to muscarine proceeded unexceptionally. Thus, treatment of the lactone 5 (eq 3) with dimethylamine (C_6H_6, 25 °C,



6 7 1 (3)

(1) W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, 1035 (1980).
(2) (a) C. H. Eugster, *Adv. Org. Chem.*, **2**, 427 (1960); (b) S. Wilkinson, *Q. Rev., Chem. Soc.*, **15**, 153 (1961); (c) J. Whiting, Y.-K. Au-Young, and B. Belleau, *Can. J. Chem.*, **50**, 3322 (1972); (d) P.-C. Wang, Z. Lysenko, and M. M. Joullie, *Tetrahedron Lett.*, 1657 (1978); (e) T. Matsumoto, A. Ichihara, and N. Ito, *Tetrahedron*, **25**, 5889 (1969); (f) A. M. Mubarak and D. M. Brown, *Tetrahedron Lett.*, 2453 (1980).
(3) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
(4) C. Kaneko, A. Sugimoto, and S. Tanaka, *Synthesis*, 876 (1974).
(5) The kinetic requirement here is that elimination of acetate from the monoalkoxide to yield 2 be faster than the addition of methyl Grignard to the second acetate and furthermore that the addition of methyl Grignard to 4 be slow.
(6) The choice of solvent was particularly important (Et_2O gave large proportions of double-addition product even at partial conversion while THF gave good yields of the monoaddition product but poor asymmetric induction).
(7) Thin-layer chromatogram (silica gel, 40% ethyl acetate in petroleum ether): 4, R_f 0.20; 5-epi-4, R_f 0.35; double addition product, R_f 0.10.
(8) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(9) All yields refer to pure, chromatographed, and fully characterized materials.

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