reproduces the empirical RE values ($\beta \simeq -16$ kcal mol^{-1}) is far smaller than the values derived by other correlations such as ionization potentials versus energies of the highest occupied MOs.[8] The reason for this is given by the fact that, as is shown in eq 11, the proportionality constant is not β_b but B given by eq 7: using $b = 4.5$ Å^{-1} and $r_0 = 1.520$ Å,[9] we have $B = 0.57\beta_b$.

Schaad and Hess[10] have given a rationalization for the use of the simple HMO method that takes into account only the π-bonding energy in calculating RE by demonstrating that for each bond both the σ-compression energy and the π-bonding energy are approximately linear functions of π-bond order. They have actually shown that the constant-β HMO method can reproduce well Dewar's RE[11,12] if, following Dewar, one uses a polyene reference structure. However, their results show erroneously that the σ-compression energy favors a distorted and localized structure.

---

(10) Schaad, L. J.; Hess, A., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3068.

(11) Dewar, M. J. S.; Gleicher, G. J. *J. Am. Chem. Soc.* **1965**, *87*, 685, 692.

(12) Dewar, M. J. S.; de Llano, C. *J. Am. Chem. Soc.* **1969**, *91*, 789.

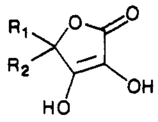
Synthetic Approaches to 4-Spiro-2-hydroxytetronic Acids[1]

Donald T. Witiak* and Ashok K. Tehim

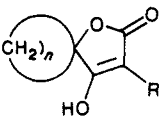
Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received December 30, 1986

Tetronic acids are components of numerous natural products,[2] including chlorothricin,[3,4] (−)-vertinolide,[5] ircinianin,[6] hippospongin,[7] and ionophore M 139603,[8] of contemporary interest. The aci-reductone 2-hydroxytetronic acid system 1 found in chlorothricin[3,4] and ascorbic acid[2] has received considerably less attention. Discovery of the antiaggregatory and antilipidemic properties of the 4-(4-chlorophenyl) analogue 2[9] provided the impetus for us to investigate mechanism-based,[10] structure–activity relationships. The early work of Dahn et al.[11] on the synthesis of aci-reductones employing a benzoin condensation is only applicable for the preparation of 4-aryl-2-hydroxytetronic acids. We investigated synthesis of spiro targets 4 and 5 with a view toward development of a general approach to the preparation of 4,4-disubstituted analogues.

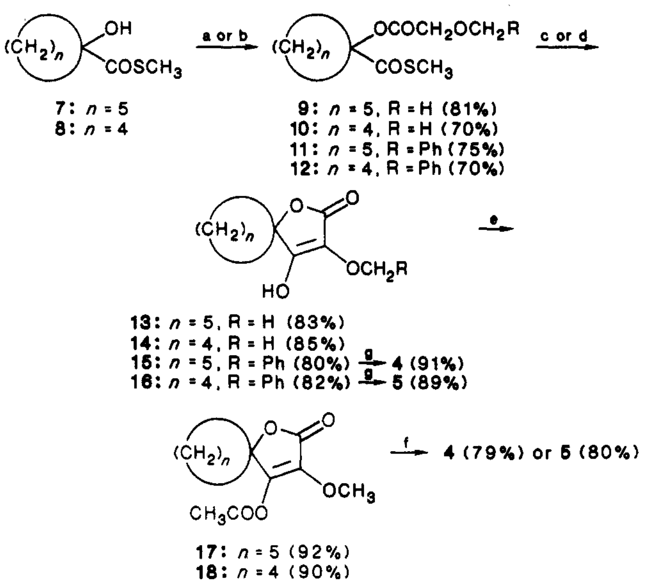


1: $R_1 = R_2 = H$
2: $R_1 = H$, $R_2 = p\text{-}ClC_6H_4$
3: $R_1 = R_2 = Me$



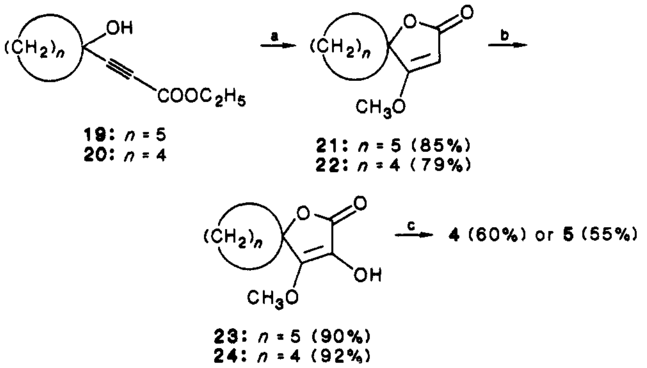
4: $n = 5$, R = OH
5: $n = 4$, R = OH
6: $n = 5$, R = H

Scheme I[a]



[a] Reagents and conditions: (a) n-BuLi, CH_3OCH_2COCl, reflux, 1 h; (b) n-BuLi, $PhCH_2OCH_2COCl$, reflux, 1 h; (c) LDA, −78 °C to room temperature, 2 h; (d) lithium hexamethyldisilazide (LiHMDA), −78 °C to room temperature, 2 h; (e) Ac_2O, Py; (f) BBr_3, CH_2Cl_2, −78 °C to room temperature, 2 h; (g) Pd/C (10%), cyclohexene, reflux, 15 min.

Scheme II[a]



[a] Reagents and conditions: (a) NaOMe, MeOH, room temperature, 6 h: (b) LDA, −78 °C (0.5 h), $B(OMe)_3$ (0.5 h), AcOH, H_2O_2 (30%); (c) HBr (48%), 45 °C.

2-Hydroxy derivative 4 previously had been prepared by Schank and Blattner[12] from the corresponding spiro-

---

(1) Support of this work by National Heart, Lung, and Blood Institute Grant No. HL-12740 is acknowledged.

(2) (a) Haynes, L. J.; Plimmer, J. R. *Q. Rev. Chem. Soc.* **1960**, 292–315. (b) Rao, Y. S. *Chem. Revs.* **1976**, *76*, 625–694. (c) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133–198.

(3) Berdy, J. In *Handbook of Antibiotic Compounds*; CRC: Boca Raton, FL, 1980; Vol. II, p 415.

(4) (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041–3052. (b) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635–648.

(5) (a) Trifonov, L. S.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Helv. Chim. Acta* **1981**, *64*, 1843–1846. (b) Trifonov, L.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Rast D. M.; Hoesch, L. *Tetrahedron* **1982**, *38*, 397–403. (c) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761–3764.

(6) (a) Hofheinz, W.; Schönholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367–1370. (b) Gregson, R. P.; Ouvrier, D. *J. Nat. Prod.* **1982**, *45*, 412–414. (c) Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *27*, 3903–3906.

(7) Kobayashi, J.; Ohizumi, Y.; Nakamura, H. *Tetrahedron Lett.* **1986**, *27*, 2113–2116.

(8) Doherty, A. M.; Ley, S. V. *Tetrahedron Lett.* **1986**, *27*, 105–108.

(9) Witiak, D. T.; Kokrady, S. S.; Patel, S. T.; Huzoor-Akbar; Feller, D. R.; Newman, H. A. I. *J. Med. Chem.* **1982**, *25*, 90–93.

(10) Witiak, D. T.; Kim, S. K.; Romstedt, K.; Newman, H. A. I.; Feller, D. R. *J. Med. Chem.* **1986**, *29*, 2170–2174.

(11) (a) Dahn, H.; Lawendel, J. S.; Hoegger, E. F.; Schenker, E. *Helv. Chim. Acta* **1954**, *37*, 1309–1318. (b) Dahn, H.; Lawendel, J. S. *Helv. Chim. Acta* **1954**, *37*, 1318–1327. (c) Dahn, H.; Hauth, H. *Helv. Chim. Acta* **1956**, *39*, 1366–1370.

(12) Schank, K.; Blattner, R. *Chem. Ber.* **1981**, *114*, 1958–1962.

0022-3263/87/1952-2324$01.50/0

tetronic acid **6** via a four-step sequence involving diazo transfer, conversion to the 2-acetoxy-2-chloro compound, reduction, and hydrolysis. Ireland and Thompson[4a] synthesized the 4,4-dimethyl analogue **3**, a model for the spiro 2-hydroxytetronic acid found in chlorothricin, in three steps (33% overall yield) from methyl 2-hydroxyisobutyrate via intramolecular Claisen condensation of its methoxyacetyl derivative.

Our synthesis for 4-spiro-2-hydroxytetronic acids (**4**, **5**), based upon the Claisen condensation, is found in Scheme I. Starting hydroxy thiomethyl esters[13] **7** and **8** are available in excellent yield[14] from cycloalkanones, whereas the corresponding hydroxy esters are available only in modest yield.[15,16]

Methoxyacetylation of tertiary alcohols **7** and **8** was best effected (81 and 70% yields, respectively) by generating the alkoxide ion with *n*-BuLi[17] followed by reaction with methoxyacetyl chloride. Similar to the Ireland–Thompson procedure,[4a] we converted **9** and **10** to the spiro tetronic acids **13** and **14** in 83 and 85% yields, respectively. Acetylation afforded **17** (92%) and **18** (90%), respectively, which upon deprotection produced **4** (79%) and **5** (80%). Preferably, cyclization of (phenylmethoxy)acetyl derivatives **11** and **12** with lithium hexamethyldisilazide (LiHMDA) provided Claisen products **15** (80%) and **16** (82%), respectively, and these materials were converted directly to the aci-reductone targets **4** (91%) and **5** (89%) under transfer hydrogenation conditions.[18]

An even shorter and cleaner sequence based upon generation of vinyl carbanions is summarized in Scheme II. Thus, known hydroxy acetylenic esters[19] **19** and **20** underwent methoxide ion induced Michael type addition–lactonization[20,21] to give tetronates **21** (85%) and **22** (79%), respectively. Under our conditions (addition reverse to those leading to isoaspertetronins[20]), we did not detect any (E)-α,β-unsaturated ester intermediates, likely owing to isomerization and trapping of the *Z* geometry as cyclized tetronates (**21**, **22**). This approach is anticipated to be superior[20] on a large scale to the Miyata and Schmidt[22] synthesis involving selective kinetic deprotonation at the β-carbon of methyl (E)-β-methoxyacrylate followed by condensation with cyclohexanone.

Impetus for the conversion of tetronates **21** and **22** to 2-hydroxytetronic acids was provided by the work of Miyata and Schmidt,[22] who showed that the vinyl carbanion (LDA, −78 °C) at the 2-position of **21** undergoes reaction with numerous electrophiles in 60–90% yield. However, reaction with the oxygen electrophile dibenzoyl peroxide produced the 2-benzyloxy derivative in only 6% yield. In order to circumvent low yields of vinylic oxygenation,[23] we employed borate ester formation followed by oxidation.[24,25] Thus, the vinyl carbanion generated (LDA, −78 °C) from **21** and **22** underwent reaction with trimethyl borate; peroxide oxidation followed by hydrolysis in one pot afforded 2-hydroxytetronates **23** (90%) and **24** (92%). Hydrolysis (48% HBr)[26] afforded 2-hydroxytetronic acids **4** (60%) and **5** (55%), respectively.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Bruker HX-90E spectrometer. Chemical shifts are reported in δ relative to tetramethylsilane in $CDCl_3$ or to the solvent lock signal at δ 2.49 in Me_2SO-d_6. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***S*-Methyl 1-(Methoxyacetoxy)-1-cyclohexanethiocarboxylate (9).** To a stirred solution (room temperature) of 0.28 g (1.6 mmol) of *S*-methyl 1-hydroxy-1-cyclohexanethiocarboxylate[13] (**7**) in 4 mL of dry THF was added dropwise 1.1 mL (1.76 mmol) of 1.6 M *n*-butyllithium in hexane. After 0.5 h, the resulting solution was treated dropwise, over a period of 5 min, with 0.16 mL (1.75 mmol) of methoxyacetyl chloride in 4 mL of THF. The resulting solution was brought to reflux for 1 h, cooled to 0 °C in an ice bath, and hydrolyzed by the addition of 10 mL of H_2O. The aqueous phase was extracted with three 15-mL portions of Et_2O, and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica gel using CH_2Cl_2 as eluant to give methoxyacetyl derivative **9** (0.32 g, 81%) as a colorless oil: IR (film) 1685 (C═O), 1760 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.4 (m, 13 H, SCH_3, $(CH_2)_5$), 3.48 (s, 3 H, OCH_3), 4.10 (s, 2 H, CH_2). Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.36; S, 13.02. Found: C, 53.61; H, 6.99; S, 13.25.

***S*-Methyl 1-(Methoxyacetoxy)-1-cyclopentanethiocarboxylate (10).** Treatment of *S*-methyl 1-hydroxy-1-cyclopentanethiocarboxylate[13] (**8**; 0.064 g, 0.4 mmol) with 1.6 M *n*-butyllithium (0.28 mL, 0.45 mmol) followed by methoxyacetyl chloride (0.04 mL, 0.44 mmol) and workup as before gave **10** (0.065 g, 70%) as a colorless oil: IR (film) 1690 (C═O), 1760 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.4 (m, 11 H, SCH_3, $(CH_2)_4$), 3.45 (s, 3 H, OCH_3), 4.05 (s, 2 H, CH_2). Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94; S, 13.80. Found: C, 51.70; H, 6.47; S, 13.27.

***S*-Methyl 1-[(Phenylmethoxy)acetoxy]-1-cyclohexanethiocarboxylate (11).** To a stirred solution (room temperature) of 0.07 g (0.4 mmol) of *S*-methyl 1-hydroxy-1-cyclohexanethiocarboxylate[13] (**7**) in 1 mL of THF was added dropwise 0.28 mL (0.45 mmol) of 1.6 M *n*-butyllithium in hexane. After 0.5 h, the resulting solution was treated dropwise, over a period of 5 min, with 0.07 mL (0.44 mmol) of (phenylmethoxy)acetyl chloride in 2 mL of THF. The resulting solution was brought to reflux for 1 h, cooled to 0 °C in an ice bath, and hydrolyzed by the addition of 5 mL of H_2O. The aqueous phase was extracted with three 10-mL portions of Et_2O, and the combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica gel using petroleum ether–CH_2Cl_2 (60:40) as eluant, affording (phenylmethoxy)acetyl derivative **11** (0.097 g, 75%) as a colorless oil: IR (film) 1690

---

(13) Knapp, S.; Trope, A. F.; Theodore, M. S.; Hirata, N.; Barchi, J. J. *J. Org. Chem.* **1984**, *49*, 608–614.

(14) Damon, R. E.; Luo, T.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, 2749–2752.

(15) Harnden, M. R. *J. Chem. Soc. C* **1969**, 960–964.

(16) Kuhl, P.; Mühlstadt, M.; Graefe, J. *Synthesis* **1976**, 825–826.

(17) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198–1199.

(18) Anantharamaiah, G. M.; Sivanandaiah, K. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 490–491.

(19) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28–29.

(20) Clemo, N. G.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2407–2411.

(21) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413–4416.

(22) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793–1796.

(23) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1–360.

(24) (a) Hawthorne, M. F. *J. Org. Chem.* **1957**, *22*, 1001. (b) Hornfeldt, A. B.; Gronowitz, S. *Ark. Kemi* **1963**, *21*, 239–257; *Chem. Abstr.* **1963**, *59*, 13917b. (c) Lumma, W. C., Jr.; Dutra, G. A.; Voeker, C. A. *J. Org. Chem.* **1970**, *35*, 3442–3444. (d) Kidwell, R. L.; Murphy, M.; Darling, S. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 918–921. (e) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 799–808.

(25) Schmidt and Hirsenkorn have also employed a borate ester to prepare a 2-hydroxytetronic acid intermediate for chlorothricolide synthesis: Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, 4357–4360. Reaction conditions differ from ours, and comparison cannot be made since the yield is not listed and the reactant differs markedly.

(26) This hydrolysis (unsuccessful with 10–25% HCl solutions) likely involves nucleophilic addition of H_2O at C_3 followed by elimination of MeOH rather than O-demethylation. O-Demethylation reactions employing Me_3SiI (2 equiv) with **23** or **24** or protection of the C-2 hydroxyl group as the acetate and subsequent use of Me_3SiI or *n*-PrSLi/HMPA were not useful for the conversion of these substances to targets **4** and **5**, respectively.

(C=O), 1765 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3–2.5 (m, 13 H, SCH_3, $(CH_2)_5$), 4.17 (s, 2 H, OCH_2O), 4.66 (s, 2 H, OCH_2Ar), 7.3–7.5 (m, 5 H, ArH). Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.33; H, 6.88; S, 9.94. Found: C, 63.70; H, 6.93; S, 9.46.

***S*-Methyl 1-[(Phenylmethoxy)acetoxy]-1-cyclopentanethiocarboxylate (12).** Treatment of *S*-methyl 1-hydroxy-1-cyclopentanethiocarboxylate[13] (8; 0.07 g, 0.44 mmol) with 1.6 M *n*-butyllithium (0.3 mL, 0.48 mmol) followed by (phenylmethoxy)acetyl chloride (0.08 mL, 0.5 mmol) and workup as before gave **12** (0.094 g, 70%) as a colorless oil: IR (film) 1685 (C=O), 1760 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6–2.5 (m, 11 H, SCH_3, $(CH_2)_4$), 4.15 (s, 2 H, OCH_2O), 4.65 (s, 2 H, OCH_2Ar), 7.3–7.5 (m, 5 H, ArH). Anal. Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54; S, 10.40. Found: C, 62.66; H. 6.79; S, 10.45.

4-Hydroxy-3-methoxy-1-oxaspiro[4.5]dec-3-en-2-one (13). To a stirred solution (−78 °C) of 0.21 mmol of LDA in 3 mL of dry THF (0.13 mL of 1.6 M *n*-butyllithium in hexane and 0.03 mL of diisopropylamine) under an argon atmosphere was added dropwise a solution of 0.025 g (0.1 mmol) of **9** in 1 mL of THF. The resulting mixture was allowed to stir at −78 °C for 1 h, slowly warmed to room temperature during 1 h, cooled to −78 °C, and quenched with 5 mL of saturated NH_4Cl solution. The resulting solution was warmed to room temperature and extracted with Et_2O (15 mL). The aqueous extract was acidified with cold 10% HCl solution and extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ extracts were combined and dried (Na_2SO_4). Removal of solvents in vacuo followed by recrystallization from acetone–petroleum ether afforded 0.017 g (83%) of crystalline tetronic acid **13**: mp 154–155 °C; IR (KBr) 1650 (C=C), 1720 (C=O), 3000 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5–2.0 (m, 10 H, $(CH_2)_5$), 3.83 (s, 3 H, OCH_3). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.31; H, 7.20.

4-Hydroxy-3-methoxy-1-oxaspiro[4.4]non-3-en-2-one (14). In a manner similar to that described above for the preparation of tetronic acid **13**, a solution of 0.228 g (0.98 mmol) of ester **10** in 4 mL of dry THF was treated with 2.1 mmol of LDA in 16 mL of THF. After the usual workup, recrystallization from acetone–petroleum ether gave **14** (0.153 g, 85%) as colorless prisms: mp 79–80 °C; IR (KBr) 1650 (C=C), 1720 (C=O), 3020 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6–2.5 (m, 8 H, $(CH_2)_4$), 3.79 (s, 3 H, OCH_3), 8.60 (brs, 1 H, OH). Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.65; H, 6.63.

4-Hydroxy-3-(phenylmethoxy)-1-oxaspiro[4.5]dec-3-en-2-one (15). To a stirred solution (−78 °C) of 0.16 mL (0.16 mmol) lithium hexamethyldisilazide (LiHMDA, 1.0 M)) dissolved in 4 mL of THF under an argon atmosphere was added dropwise a solution of 0.025 g (0.08 mmol) of (phenylmethoxy)acetyl derivative **11** in 1 mL of THF. The resulting mixture was allowed to stir at −78 °C for 1 h, warmed to room temperature for 1 h, cooled to −78 °C, and quenched with 5 mL of saturated NH_4Cl solution. The resulting mixture was then warmed to room temperature and extracted with Et_2O (15 mL). The aqueous extract was acidified with cold 10% HCl solution and extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ extracts were combined and dried (Na_2SO_4). Solvent removal in vacuo, followed by recrystallization from acetone–petroleum ether, gave 0.017 g (80%) of crystalline tetronic acid **15**: mp 171–172 °C; IR (KBr) 1630 (C=C), 1725 (C=O), 3020 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$ + CD_3COCD_3) δ 1.35–1.92 (m, 10 H, $(CH_2)_5$), 5.05 (s, 2 H, CH_2), 7.26–7.48 (m, 5 H, ArH). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.96; H, 6.79.

4-Hydroxy-3-(phenylmethoxy)-1-oxaspiro[4.4]non-3-en-2-one (16). Treatment of (phenylmethoxy)acetyl derivative **12** (0.534 g, 1.73 mmol) with 3.63 mL (3.63 mmol) of a 1 M solution of LiHMDA in THF, followed by workup as described previously and recrystallization from acetone–petroleum ether afforded **16** (0.37 g, 82%) as colorless prisms: mp 144–145 °C; IR (KBr) 1615 (C=C), 1725 (C=O), 3025 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$ + CD_3COCD_3) δ 1.6–2.0 (m, 8 H, $(CH_2)_4$), 5.05 (s, 2 H, CH_2), 7.2–7.5 (m, 5 H, ArH). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.25; H, 6.44.

4-Acetoxy-3-methoxy-1-oxaspiro[4.5]dec-3-en-2-one (17). To a stirred solution (0 °C) of 0.025 g (0.13 mmol) of the tetronic acid **13** in 1.5 mL of dry CH_2Cl_2 containing 0.021 mL (0.26 mmol) of dry pyridine was added 0.024 mL (0.25 mmol) of Ac_2O. The resulting mixture was stirred for 12 h at room temperature under an argon atmosphere. Concentration of solvents in vacuo, followed by recrystallization from CH_2Cl_2–petroleum ether gave 0.028 g (92%) of crystalline enol acetate **17**: mp 100–101 °C; IR (KBr) 1690 (C=C), 1765 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5–1.9 (m, 10 H, $(CH_2)_5$), 2.30 (s, 3 H, OAc), 3.92 (s, 3 H, OCH_3). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.90; H, 6.76.

4-Acetoxy-3-methoxy-1-oxaspiro[4.4]non-3-en-2-one (18). Treatment of tetronic acid **14** (0.025 g, 0.14 mmol) with pyridine (0.023 mL, 0.28 mmol) and Ac_2O (0.026 mL, 0.28 mmol) followed by workup as previously described gave **18** (0.276 g, 90%) as colorless needles: mp 79–80 °C; IR (KBr) 1690 (C=C), 1760 (C=O), 1780 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6–2.1 (m, 8 H, $(CH_2)_4$), 2.30 (s, 3 H, OAc), 3.93 (s, 3 H, OCH_3). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.25; H, 6.49.

4-Methoxy-1-oxaspiro[4.5]dec-3-en-2-one (21). To a stirred solution (room temperature) of 7.0 g (35.7 mmol) of 1-(2-carbethoxyethynyl)cyclohexanol[19] (**19**) in 35 mL of MeOH under an argon atmosphere was added dropwise 60 mL of NaOMe solution (25% by weight in MeOH). The resulting mixture was allowed to stir at room temperature for 6 h, concentrated in vacuo and diluted with 75 mL of ice-cold H_2O. The resulting solid was filtered and dried. Additional compound was obtained by acidifying the mother liquor with 25% HCl solution and extracting with Et_2O (50 mL). The organic phase was washed with Na_2CO_3 solution (10%, 3 × 20 mL) followed by brine, dried (Na_2SO_4), and concentrated. The residue was added to the solid and recrystallized from petroleum ether–CH_2Cl_2 to give tetronate **21** (5.5 g, 85%) as colorless prisms, mp 105–106 °C (lit.[22] mp 103–104 °C).

4-Methoxy-1-oxaspiro[4.4]non-3-en-2-one (22). Treatment of 1-(2-carbethoxyethynyl)cyclopentanol[19] (**20**; 5.2 g, 28.5 mmol) with 20 mL of NaOMe solution (25% by weight in MeOH) followed by workup as previously described and recrystallization from petroleum ether–CH_2Cl_2 gave crystalline tetronate **22** (3.8 g, 79%), mp 63–64 °C (lit.[27] mp 64–65 °C).

3-Hydroxy-4-methoxy-1-oxaspiro[4.5]dec-3-en-2-one (23). To a stirred solution (−78 °C) of 28.8 mmol of LDA in 80 mL of THF (18.0 mL of 1.6 M *n*-butyllithium in hexane and 4.03 mL of diisopropylamine) under an argon atmosphere was added dropwise a solution of 4.4 g (24.2 mmol) of tetronate **21** in 30 mL of THF. The resulting mixture was allowed to stir at −78 °C for 0.5 h. Following dropwise addition of trimethyl borate (4.1 mL, 36.1 mmol) in THF (10 mL), the mixture (−78 °C) was stirred for an additional 0.5 h. The mixture was treated with AcOH (4.0 mL, 70.0 mmol) and then H_2O_2 solution (30%, 4.0 mL, 39.2 mmol) and allowed to warm to room temperature. A saturated solution of $NaHCO_3$ (60 mL) was added, and the mixture was stirred for an additional 0.5 h. Et_2O (160 mL) was added, and the organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 30 mL) followed by brine (2 × 30 mL) and then dried (Na_2SO_4). Removal of the solvents in vacuo followed by recrystallization from petroleum ether–CH_2Cl_2 gave 4.3 g (90%) of crystalline 2-hydroxytetronate **23**: mp 129–130 °C; IR (KBr) 1700 (C=C), 1750 (C=O), 3330 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4–2.0 (m, 10 H, $(CH_2)_5$), 4.16 (s, 3 H, OCH_3), 5.78 (brs, 1 H, OH). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.47; H, 7.28.

3-Hydroxy-4-methoxy-1-oxaspiro[4.4]non-3-en-2-one (24). Treatment at −78 °C of tetronate **22** (4.07 g, 24.2 mmol) with 28.8 mmol of LDA in THF (80 mL), trimethyl borate (4.1 mL, 36.1 mmol), AcOH (4.0 mL, 70.0 mmol), and H_2O_2 solution (30%, 4.0 mL, 39.2 mmol) followed by workup as previously described and recrystallization from petroleum ether–CH_2Cl_2 afforded 2-hydroxytetronate **24** (4.1 g, 92%) as colorless prisms: mp 125–126 °C; IR (KBr) 1675 (C=C), 1745 (C=O), 3280 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.5–2.2 (m, 8 H, $(CH_2)_4$), 4.19 (s, 3 H, OCH_3), 5.86 (brs, 1 H, OH). Anal. Calcd for $C_9H_{12}O_4$: C, 58.71; H, 6.69.

3,4-Dihydroxy-1-oxaspiro[4.5]dec-3-en-2-one (4). Method I. To a stirred solution (−78 °C) of 0.025 g (0.1 mmol) of the enol acetate **17** in 1.0 mL of CH_2Cl_2 under an argon atmosphere was added dropwise 0.52 mL (0.52 mmol) of a 1 M solution of BBr_3 in CH_2Cl_2. The resulting mixture was allowed to stir for 1 h at −78 °C, warmed to room temperature during 1 h, cooled to −78 °C, and quenched with 5 mL of saturated NH_4Cl solution. The

---

(27) Carlson, R. M.; Peterson, J. R.; Hoop, B.; Jensen, K. J. *Synth. Commun.* **1982**, *12*, 977–982.

resulting solution was then warmed to room temperature and was extracted with $CHCl_3$ (15 mL). The $CHCl_3$ solution was extracted with $NaHCO_3$ solution (10%, 2 × 5 mL), acidified with cold 10% HCl solution, and extracted with $CHCl_3$ (2 × 10 mL). The organic extracts were dried (Na_2SO_4) and the solvents removed in vacuo. Recrystallization of the residue from acetone–petroleum ether afforded 0.015 g (79%) of 2-hydroxytetronic acid **4**, mp 238–239 °C (lit.[12] mp 235 °C).

Method II. To a solution of 2-(phenylmethoxy)tetronic acid **15** (0.05 g, 0.18 mmol) in EtOH (4 mL) were added 10% Pd/C (0.05 g) and cyclohexene (0.37 mL, 3.6 mmol). The resulting mixture was refluxed for 15 min under argon, filtered, and concentrated in vacuo and the residue taken up in Et_2O (30 mL). The Et_2O solution was extracted with $NaHCO_3$ solution (10%, 2 × 10 mL), which was acidified with cold 10% HCl solution and extracted with $CHCl_3$ (2 × 10 mL). The $CHCl_3$ extracts were combined and dried (Na_2SO_4). Removal of the solvents in vacuo, followed by recrystallization from acetone–petroleum ether, gave 0.031 g (91%) of 2-hydroxytetronic acid **4**.

Method III. 2-Hydroxytetronate **23** (4.0 g, 20.2 mmol) was stirred with HBr solution (48%, 80.0 mL) at 45 °C for 12 h. The reaction mixture was diluted with ice-cold H_2O (300 mL) and extracted with Et_2O (100 mL). The organic extract was extracted with $NaHCO_3$ solution (10%, 3 × 50 mL), which was acidified with cold 10% HCl solution. The resulting solid was filtered, dried, and recrystallized from acetone–petroleum ether to give crystalline 2-hydroxytetronic acid **4** (2.2 g, 60%).

3,4-Dihydroxy-1-oxaspiro[4.4]non-3-en-2-one (5). Method I. Treatment of the enol acetate **18** (0.02 g, 0.09 mmol) with a 1 M solution of BBr_3 in CH_2Cl_2 (0.44 mL, 0.44 mmol), followed by the workup for **4** (method I) and recrystallization from acetone–petroleum ether, gave 0.012 g (80%) of 2-hydroxytetronic acid **5**: mp 211–212 °C; IR (KBr) 1640 (C=C), 1728 (C=O), 3320 (OH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.4–2.2 (m, 8 H, $(CH_2)_4$), 3.34 (brs, 1 H, OH), 10.16 (very brs, 1 H, OH). Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.53; H, 5.84.

Method II. Treatment of 2-(phenylmethoxy)tetronic acid **16** (0.05 g, 0.19 mmol) with 10% Pd/C (0.05 g) and cyclohexene (0.39 mL, 3.8 mmol), followed by the workup for **4** (method II) and recrystallization from acetone–petroleum ether, afforded 0.029 g (89%) of 2-hydroxytetronic acid **5**.

Method III. Treatment of 2-hydroxytetronate **24** (4.0 g, 21.7 mmol) with HBr solution (48%, 55.0 mL) at 45 °C for 12 h, followed by the workup for **4** (method III) and recrystallization from acetone–petroleum ether, gave 2.03 g (55%) of 2-hydroxytetronic acid **5**.

Stereospecificity of the Photorearrangement of Nitronate Anions and Its Utilization for Stereospecific Cleavage of Cyclic Compounds

Kazutoshi Yamada,* Keiki Kishikawa, and
Makoto Yamamoto

Department of Industrial Chemistry, Faculty of Engineering, Chiba University, Chiba-shi, 260 Japan

Received November 13, 1986

We have reported high regioselectivity of the photorearrangement of nitronate anions in preceding papers.[1-3] The nitronate anions are transformed to hydroxamic acids by irradiation with a low-pressure mercury lamp. These rearrangements are controlled by the number of substituents at the β-carbon atoms, and in the case of the same number of substituents the β-carbon atom with an electron-withdrawing group migrates to the nitrogen atom.

Scheme I

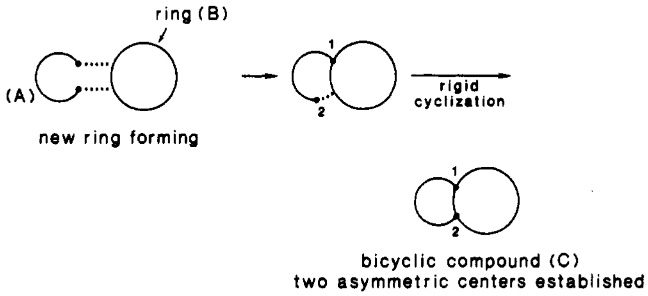


Table I. Retention of the Photorearrangement

entry	chemical yield,[a] %	ratio of the major diastereomer: before reaction, % (form)	ratio of the major diastereomer: after reaction, % (form)
1	14	91[b] (*R*)	90
2	47	99 (**2a**)	99 (**2b**)
3	81	96 (**3a**)	99 (**3b**)
4	62	99 (**4a**)	99 (**4ab**)
5	42	99 (**5a**)	99 (**5b**)

[a] Isolated yield. [b] Ratio of the major enantiomer.

In the synthesis of organic compounds having asymmetric carbons it is necessary that reactions take place regioselectively and stereospecifically. From this viewpoint, the stereospecificity of the photoreaction was investigated by using nitro compounds **1a–5a**. In all cases, the reaction showed complete retention of stereochemistry. In this manner normally inaccessible lactams such as 2-azabicyclo[3.2.1]octan-3-ones and 3-azabicyclo[3.2.1]octan-2-ones[4] were synthesized easily without loss of stereochemistry. Hydrolysis of lactams and **2c** and **3c** gave 1,3-disubstituted cyclopentane amino acid methyl esters that have several asymmetric centers.

Steric hindrance and stereoelectronic effects are effective in controlling the stereochemistry of the generated diastereomers; however, it is impossible to control them perfectly. In order to get a single diastereomer, it is necessary to choose a rigid polycyclic compound and to cleave the rings by a stereospecific method. Many natural products were synthesized by this methodolgy recently.[5-8] According to Scheme I the bicyclic compound (C) is synthesized by ring (B) and (A). If the bicyclic compound (C) is rigid and has no plane of symmetry, the number (k) of asymmetric centers is $2(N - 1)$ (N equals the number of rings). For example, bicyclic compound **2a** can exist in only the 1*R*,4*S* or 1*S*,4*R* form, as the 1*S*,4*S* and 1*R*,4*R* forms would be impossibly strained. So rigid bicyclo[2.2.1]heptanes have a pair of asymmetric centers ($k = 2(2 - 1) = 2$). Similarly **3a–5a** have two asymmetric carbons produced by the relationship.

Compound **1a** (82% ee[9]), prepared by the method of Mukaiyama et al.,[10] was irradiated in sodium meth-

---

[1] Yamada, K.; Kanekiyo, T.; Tanaka, S.; Naruchi, K.; Yamamoto, M. *J. Am. Chem. Soc.* **1981**, *103*, 7003–5.

[2] Yamada, K.; Tanaka, S.; Naruchi, K.; Yamamoto, M. *J. Org. Chem.* **1982**, *47*, 5283–9.

[3] Kikuchi, O.; Kanekiyo, T.; Tanaka, S.; Naruchi, K.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1509–13.

[4] (a) Nakazaki, M.; Naemura, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 532–5. (b) Noyes, W. A.; Potter, R. S. *J. Am. Chem. Soc.* **1915**, *37*, 189–203. (c) Fox, L. B.; Rosenberg, H. M. *J. Chem. Soc. D* **1969**, 1115. (d) Kozlov, N. G.; Pehk, T. *Zh. Org. Khim.* **1982**, *18*, 1118–9. (e) Krow, G. R.; Szczepanski, S. *Tetrahedron Lett.* **1980**, *21*, 4593–6.

[5] Tufariello, J. J.; Mullen, G. B.; Tegler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. K. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435.

[6] Ogawa, S.; Takagaki, T. *J. Org. Chem.* **1985**, *50*, 2356–9.

[7] Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049–51.

[8] Oppolzer, W.; Petrzilka, M. *J. Am. Chem. Soc.* **1976**, *98*, 6722.

[9] Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.* **1971**, *93*, 5913.

[10] Takeda, T.; Hoshiko, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 797.

0022-3263/87/1952-2327$01.50/0