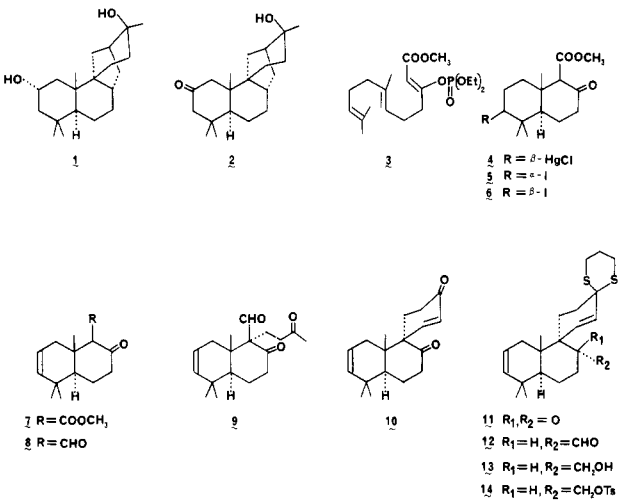
Acknowledgment. The support of Research Grant GM 22969 from the National Institutes of Health is most gratefully acknowledged. We also thank Dr. John M. Wright for his help with the ^{31}P instrumentation and Wayne J. Becktel for helpful discussions.

Deborah B. Lerner, David R. Kearns*
Department of Chemistry, University of California
San Diego, La Jolla, California 92093
Received June 30, 1980

Total Synthesis of (±)-Stemodin and (±)-Stemodinone

Sir:

The tetracyclic diterpenes stemodin (**1**) and stemodinone (**2**),



obtained from the leaves of *Stemodia maritima* L. (Jamaican "sea mint"),[1] are structurally related to the antiviral and antimitotic fungal metabolite aphidicolin,[2] differing mainly in the stereorelationship of the C and D rings. Subsequent to the completion of the total synthesis of (±)-aphidicolin,[3] we have undertaken cognate studies in the stemodin series. Successful stereoselective syntheses of racemic **1** and **2** have now been realized by the approach which is outlined herein.

Enol phosphate **3**[4] was treated at −20 °C in anhydrous nitromethane with 1.2 equiv of mercuric trifluoroacetate[3] in the same solvent. Warming to 0 °C followed by treatment with aqueous sodium chloride gave bicyclic ketoester **4** [mp 179–181 °C; IR_{max} ($CHCl_3$) 1760, 1725 cm^{-1}; ^1H NMR δ 2.90 (dd, 1 H, ClHgCH, J_1 = 10 Hz, J_2 = 5 Hz)] in 60% yield along with 10–15% of monocyclic material. Replacement of chloromercury by iodide was accomplished by slow addition of 1.07 equiv of potassium triiodide to an oxygen-free solution of **4** in 90% aqueous dioxane.[5] Reductive workup with aqueous sodium bisulfite solution and ether extraction furnished in quantitative yield a mixture of 3α- and 3β-iodo keto esters **5** and **6** (5:1), R_f 0.56 and 0.49, respectively, on silica gel plates by using a single development with 25% ethyl acetate in hexane. The reaction of **4** with iodine or iodine monochloride in chloroform ($CHCl_3$) gave equal quantities of **5** and **6**. The crude mixture of iodides was treated at 23 °C for 48 h with powdered anhydrous lithium chloride in dimethylformamide (DMF) to afford after extractive workup and chromatography on silica gel the unsaturated keto ester **7** [mp 76–80 °C; IR_{max} ($CHCl_3$) 1750, 1718, 1630 cm^{-1}; ^1H NMR δ 5.4 (m, 2 H, CH=CH), 3.26 (s, 1 H, O=CCH)] in 70% overall yield from **4**.

The unsaturation in **7** allowed the introduction of oxygen at C-2 at the end of the synthesis. The conversion of **7** to keto aldehyde **8** [mp 113–116 °C; IR_{max} ($CHCl_3$) 1718, 1620–1585 cm^{-1}; ^1H NMR δ 9.01 (d, 1 H, CHO, J = 3.2 Hz)] was accomplished by the following sequence: (1) protection of the ketone as the ethylene ketal (ethylene glycol in benzene, *p*-toluenesulfonic acid, reflux, 2 h; 90%, mp 115–117 °C), (2) reduction of the carbomethoxy appendage to hydroxymethyl (lithium aluminum hydride in ether at 23 °C; 90%), (3) oxidation (pyridinium chlorochromate[6] in CH_2Cl_2 at 23 °C; 92%), (4) ketal hydrolysis (10:1:1 acetone–water–70% aqueous perchloric acid at 23 °C, 3 h; 96%). A direct method for the reduction of carbomethoxy to formyl was not found. An excess of diisobutylaluminum hydride in refluxing benzene gave no detectable reduction, perhaps as a consequence of the shielding provided by the two quaternary centers flanking the ester function.

This short and efficient preparation of rings A and B set the stage for the introduction of the spiro ring. The Michael reaction of keto aldehyde **8** at 23 °C with methyl vinyl ketone in 1:1 tetrahydrofuran (THF)–*tert*-butyl alcohol and 0.2 equiv each of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and potassium carbonate gave adduct **9** [mp 90–95 °C; IR_{max} ($CHCl_3$) 1730–1700 cm^{-1}; ^1H NMR δ 10.1 (d, 1 H, CHO, J = 1.5 Hz), 2.07 (s, 3 H, $COCH_3$)] in 70% yield, along with 20% of unreacted **8**. Aldol closure to spiro diketone **10** [mp 139–141 °C] was effected in 93% yield by using pyrrolidinium acetate[7] in THF–methanol at 23 °C. Selective reaction at the less hindered conjugated carbonyl group with bis(*S*-trimethylsilyl)propane-1,3-dithiol[8] in $CHCl_3$ at 23 °C in the presence of zinc iodide gave thioketal **11** [mp 153–154 °C] in quantitative yield.

The conversion of **11** to aldehyde **12** was accomplished by using the methodology described previously in connection with the total synthesis of aphidicolin:[3] (1) treatment of **11** with 10 equiv of trimethylsilyl cyanide[9] [87%; mp 165–167.5 °C], (2) reduction to the α-trimethylsilyloxy aldehyde [80%; mp 135–137 °C] with 4 equiv of diisobutylaluminum hydride in toluene at −10–5 °C, (3) addition of 0.95 equiv of trimethylsilyllithium[10] in ether–hexamethylphosphoramide (HMPA) at −35 °C to the formyl function (80% yield), and (4) treatment with 3 equiv of lithium diisopropylamide in THF containing 5% HMPA at 23 °C under positive argon pressure to give aldehyde **12** [IR_{max} ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 9.77 (s, 1 H, CHO)] in 80% yield after workup with aqueous acid.

The reduction of aldehyde **12** in THF–ethanol at 0 °C with sodium borohydride gave primary alcohol **13**, which was converted to tosylate **14** (*p*-toluenesulfonyl chloride, 4-(dimethylamino)-pyridine,[11] and pyridine in $CHCl_3$ at 23 °C). Thioketal cleavage by using 2.2 equiv of 1,3-diiodo-5,5-dimethylhydantoin[12] at −20 °C for 30 min in 5:5:1 acetone–THF–water produced enone tosylate **15** which was transformed to the tetracyclic ketone **16** in two steps: (1) treatment with 1.1 equiv of potassium *tert*-butoxide in THF at 23 °C, followed by (2) enone reduction by use of lithium

(1) Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705. Although syntheses of **1** and **2** have not previously been achieved, approaches to **1** and **2** have been reported: Herbert, D. J. *Diss. Abstr. Int. B.* **1980**, *40*, 5272b. Ghosal, P. K.; Mukherjee, D.; Dutta, P. C. *Tetrahedron Lett.* **1976**, 2997.

(2) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.

(3) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

(4) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.

(5) Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill, New York, 1968; pp 86–99.

(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(7) de Groot, Ae.; Jansen, B. J. M. *Tetradhedron Lett.* **1976**, 2709. Best results were obtained when an excess of acetic acid was used.

(8) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

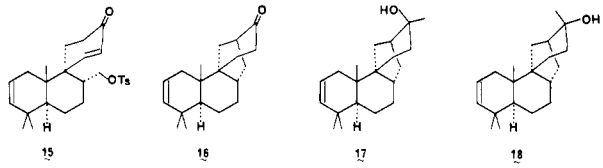
(9) (a) Parham, W. E.; Roosevelt, C. S. *Tetrahedron Lett.* **1971**, 923. (b) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55. (c) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.

(10) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063.

(11) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(12) Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101.

0002-7863/80/1502-7612$01.00/0



15 16 17 18

in liquid ammonia at −78 °C. The overall yield of **16** [mp 103–105 °C; IR_{max} ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.01 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3)] from aldehyde **12** was 50% after chromatography on silica gel.

The next task, stereospecific introduction of C-18, was problematical since examination of molecular models did not indicate a preferred direction of carbonyl addition with respect to the bicyclo[3.2.1]octanone system. Methyllithium in ether at 0 °C reacted with **16** to give a mixture (~1:1) of tertiary alcohols **17** [mp 119–122 °C] and **18** [mp 147–149 °C, sublimes], R_f 0.37 and 0.31, respectively, after one elution by using 30% THF in hexane.[13] Trimethyl aluminum,[14] lithium tetramethylaluminate, and lithium trimethylmanganate[15] were also not selective. Methylmagnesium bromide in ether at 23 °C furnished alcohols **17** and **18** in the ratio of 2.4:1 (85% yield). Nonetheless, adequate stereoselectivity was obtained with dimethylsulfoxonium methylide[16] in dimethyl sulfoxide as reagent at 23 °C. Reduction of the isomeric spiro epoxides so obtained with lithium triethylborohydride[17] in THF at 23 °C afforded cleanly **17** and **18** in a ratio of 5:1. The improved selectivity is probably a reflection of a favored product-determining elimination of dimethyl sulfoxide from one of the reversibly formed ylide–carbonyl adducts of **16**.

Treatment of **17** at 23 °C in acetone with a solution of *N*-bromoacetamide (7.6 equiv) in water[18] followed by extractive workup with methylene chloride gave a single bromohydrin which was directly oxidized to the corresponding α-bromo ketone with PCC[6] in methylene chloride and debrominated with zinc dust in ether–aqueous ammonium chloride at 23 °C to afford synthetic (±)-stemodinone (**2**) [80%; mp 199–201 °C; IR_{max} (neat) 3392, 1689 cm^{-1}; ^1H NMR δ 1.13 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3)] which was spectroscopically and chromatographically identical with natural stemodinone.[19] (±)-Stemodinone was reduced to (±)-stemodin (**1**) [mp 218–220 °C; IR_{max} (neat) 3330 cm^{-1}; ^1H NMR δ 1.12 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3)] with sodium in THF–ethanol at 0 °C in 43% overall yield from **17**.[20,21] Natural and synthetic **1** were identical by IR, ^1H NMR, and mass spectra and thin-layer chromatography in three solvent systems.[22]

(13) The stereochemistry of the tertiary alcohols **17** and **18** was assigned by comparing the observed ^1H NMR chemical shifts of the carbinol methyl groups with the reported[1] data for stemodin (**1**): δ 1.08 for stemodin, vs. 1.24 for **18** and 1.12 for **17**.

(14) Laemmle, J.; Ashby, E. C.; Roling, P. V. *J. Org. Chem.* **1973**, *38*, 2526.

(15) Posner, G. H. Ph.D. Dissertation, Harvard University, 1968, p 36.

(16) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(17) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486.

(18) Reich, H.; Reichstein, T. Helv. *Chim. Acta* **1943**, *26*, 562.

(19) We are indebted to Dr. Percy S. Manchand for generous samples of natural stemodin and stemodinone.

(20) Sodium borohydride reduced **2** to the 2β-alcohol.

(21) In connection with our synthesis see, Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979**, 622. It must be noted that our observed ^1H NMR chemical shifts of the methyl groups of 3-desoxystemodin (in $CDCl_3$) [δ 0.88 (s, 6 H, $2CH_3$), 0.96 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3)] differ from the reported data of Chatterjee [δ 0.90 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.13 (s, 3H, CH_3)]. See also Cornforth, J. *Tetrahedron Lett.* **1980**, *21*, 709.

(22) This research was assisted financially by a grant from the National Science Foundation.

E. J. Corey,* Marcus A. Tius, Jagabandhu Das

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received July 28, 1980

Solvolysis of Adamantanone Cyanohydrin Sulfonates. An Evaluation of H/α-CN vs. H/β-CN Rate Ratios

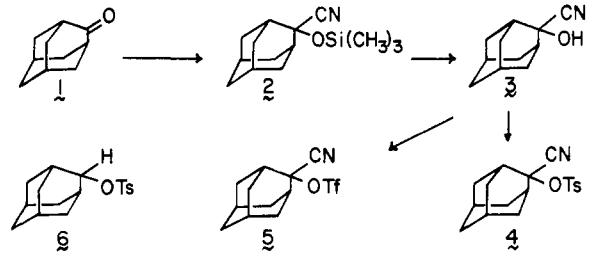
Sir:

We have recently provided both experimental[1] and theoretical[2] evidence that a cyano function attached directly to a carbocation can provide resonance stabilization which almost balances its inductive destabilization. In addition, our theoretical studies[2] suggested that an α-cyano substituent should be less destabilizing than a β-cyano substituent to an electron-deficient cationic center. These theoretical predictions could be experimentally evaluated in terms of H/α-CN vs. H/β-CN rate ratios. We now present experimental evidence which supports our theoretical calculations.

Because of its structural rigidity and its steric blockage of backside displacement of attached leaving groups by solvent, the tricyclo[3.3.1.$1^{3,7}$]decyl (adamantyl) skeleton has been widely employed as a standard substrate for the study of the properties of carbonium ions.[3,4] In view of these well-established characteristics, we felt that the adamantyl skeleton would serve as an ideal substrate for evaluating the relative effects of H, α-CN, and β-CN on the ease of ionization of sulfonate esters. Treatment of adamantanone (**1**) with trimethylsilyl cyanide and a catalytic amount of zinc iodide gave **2**, which on hydrolysis with 3 N hydrochloric acid according to our general procedure[5] gave adamantanone cyanohydrin[6] (**3**) in 95% overall yield. Addition of *p*-toluenesulfonic anhydride to **3** gave a 92% yield of **4**,[7] mp 88–90 °C. In a similar manner, **3** reacted with trifluoromethanesulfonic anhydride to give 92% of **5**, mp 48–49 °C.

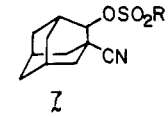
For rate comparisons, **6** was prepared according to the literature procedure.[4]

Table I lists the rates observed for the solvolysis of **4–6** in 100%



1 2 3 6 5 4

2,2,2-trifluoroethanol buffered with 2,6-lutidine[8] and of **5** in 90% aqueous acetone. As can be noted from a comparison of **4** and **6**, the H/α-CN rate ratio is 2.1×10^3. This rate ratio is extremely close to the value of 1.9×10^3 observed for cyclooctyl tosylate vs. the tosylate of cyclooctanone cyanohydrin.[1] Since Farcasiu[4g,h] has studied the solvolysis of **7** (R = CH_2CF_3) and found a H/



7

(1) P. G. Gassman and J. J. Talley, *J. Am. Chem. Soc.*, **102**, 1214, 4138 (1980).

(2) D. A. Dixon, P. A. Charlier, and P. G. Gassman, *J. Am. Chem. Soc.*, **102**, 3957 (1980).

(3) For a review see R. C. Fort, Jr., "Adamantane: The Chemistry of Diamond Molecules", P. G. Gassman, Ed., Marcel Dekker, Inc., New York, 1976, pp 164–172.

(4) (a) J. A. Bone and M. C. Whiting, *J. Chem. Soc., Chem. Commun.*, 115 (1970); (b) L. R. Pritt and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1458 (1976); (c) J. M. Harris, D. C. Clark, and J. F. Fagan, *J. Am. Chem. Soc.*, **96**, 4478 (1974); (d) D. Lenoir, R. E. Hall, and P. von R. Schleyer, *ibid.*, **96**, 2138 (1974); (e) D. Lenoir, D. J. Raber, and P. von R. Schleyer, *ibid.*, **96**, 2149 (1974); (f) J. M. Harris, A. Becker, J. F. Fagan, and F. A. Walden, *ibid.*, **96**, 4484 (1974); (g) D. Farcasiu, *ibid.*, **98**, 5301 (1976); (h) D. Farcasiu, *J. Org. Chem.*, **43**, 3878 (1978).

(5) P. G. Gassman and J. J. Talley, *Tetrahedron Lett.*, 3773 (1978).

(6) J. L. M. A. Schlatmann, J. G. Korsloot, and J. Schut, *Tetrahedron*, **26**, 949 (1970); R. M. Majerski, Z. Majerski, and E. Petsch, *J. Org. Chem.*, **40**, 3772 (1975).

(7) Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds.

(8) For the basis for the use of anhydrous 2,2,2-trifluoroethanol, see ref 1.

0002-7863/80/1502-7613$01.00/0