(±)-7 (R = H), 81799-94-2; (±)-8 (R = $CH_3$), 81767-84-2; (±)-8 (R = H), 81767-85-3; (±)-9 (R = $CH_3$), 81767-86-4; (±)-9 (R = H), 81800-03-5; (±)-10 (R = $CH_3$), 81740-50-3; (±)-10 (R = H), 81740-51-4; (±)-11 (R = $CH_3$), 81767-87-5; (±)-11 (R = H), 81767-88-6; (±)-12 (R = $CH_3$), 81753-04-0; (±)-12 (R = H), 81768-76-5; I, 5312-85-6; II, 81740-52-5; III, 81740-53-6; Va, 81740-54-7; Vb, 81740-55-8; (±)-VIa, 81740-56-9; (±)-VIb, 81740-57-0; (±)-VIIa, 81740-58-1; (±)-VIIb, 81740-59-2; (±)-VIIIa, 81740-60-5; (±)-VIIIb, 81740-61-6; (±)-IXa, 81740-62-7; (±)-IXb, 81753-05-1.

**Supplementary Material Available:** A summary of the complete scheme for the preparation of the cyclization substrates **3a**, **3b**, **4a**, and **4b** involving a number of new compounds (3 pages). Ordering information is given on any current masthead page.

## Total Synthesis of *dl*-Spironolactone and *dl*-19-Norspironolactone by Biomimetic Polyene Cyclization Methodology[1]

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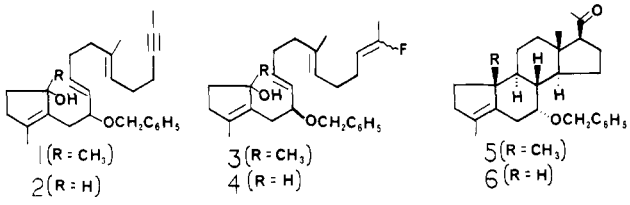
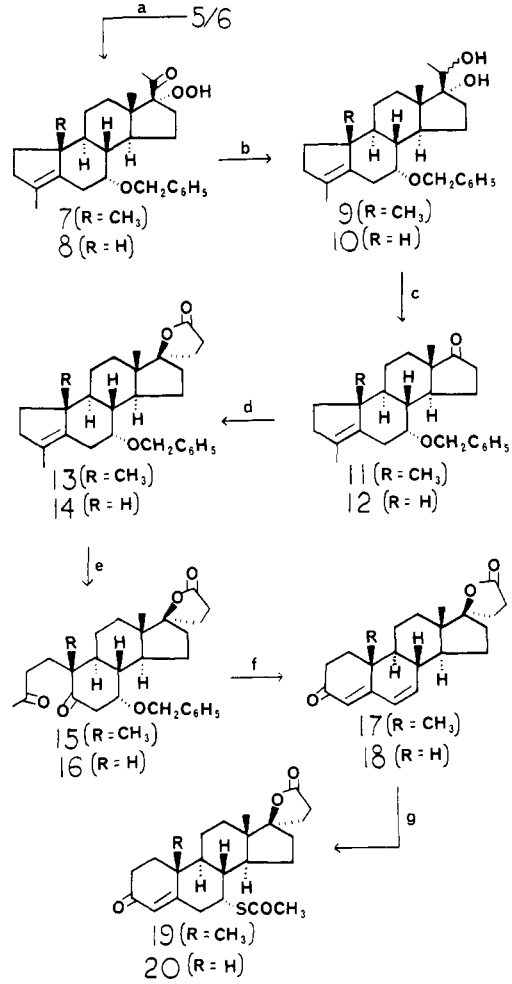
The cyclization of the substrates **1**, **2**, **3** and **4** is described in




the preceding communication.[2] The major product derived from **1** as well as from **3** was presumed to be the 7α-benzyloxy steroidal substance **5**. Similarly the principal product from either **2** or **4** was thought to be the 19-nor material **6**. We decided to try to obtain unequivocal proof of the constitution of **5** and **6** by transforming them into substances of established structure, in particular the well-known[3b] spironolactone types and intermediates leading thereto. The present communication discloses an account of these structure-proving experiments that have led also to the realization of one of the major aims of the original study, namely, the total synthesis of the racemic form of the aldosterone blocking agent, spironolactone (**19**), an important diuretic for treating severe cases of hypertension.

The synthetic transformations that were developed for conversion of **5** and **6** into the spironolactones **19** and **20**, respectively, are summarized in Scheme I. Thus **5** was submitted to base-catalyzed oxygenation,[4] giving the 17α-hydroperoxy compound **7**. Attempts to effect cleavage of this latter substance directly to the 17-keto compound[5] resulted in formation of highly impure specimens of **11**. Better results were obtained by sodium borohydride reduction of **7** to give the diol **9** as a mixture of C-20 epimers, followed by lead tetraacetate oxidation. Thus, without any purification of the intermediates **7**[7a] and **9**,[7a] the ketone **11**,[6a,7a,b] mp 77–80 °C,[7d] was produced in 58% yield from **5**.

Scheme I




[a] Excess *t*-BuOK, 4:4:1 *t*-BuOH/THF/DMF, $O_2$, 1 h, 0 °C. [b] Excess $NaBH_4$, EtOH, 2 h, 20 °C. [c] Excess $Pb(OAc)_4$, HOAc, 1 h, 20 °C. [d] 3 mol equiv of $(Me_2N)_2P(O)OCH_2CH{=}CH_2$, 5 mol equiv of 1.5 M *n*-BuLi/hexane, THF, 10 min, −60 °C; 30 m, −20 °C, then 5 mol equiv of TMEDA; **11** or **12**, 10 min, −60 °C; $NH_4Cl$. [e] Excess $O_3$, 1 mol equiv of MeOH, 0.5% $C_5H_5N$ in $CH_2Cl_2$, 20 min, −78 °C; excess Zn, HOAc. [f] 40:4:1 HOAc/concentrated $HCl/H_2O$, 65 h, 22 °C. [g] HSAc, 4 h, 29 °C.

Similarly **6** was converted via the intermediates **8**[7a] and **10**[7a] into **12**,[6a,7a,b] mp 98–102 °C[7d] (73% yield from **6**). Ketone **11** was transformed, by the elegant one-step method of Sturtz et al.,[8] into the lactone **13**,[6a,7a,b] mp 101–103 °C[7d] (68% conversion, 79% yield). Similarly **12** was converted into **14**,[6a,7a,b] mp 116–119 °C[7d] (79% yield). Lactone **13** was ozonolyzed, and the resulting crude diketo compound **15**[7a] was treated with hydrochloric acid/acetic acid at 22 °C, which effected concomitant cyclodehydration of the 1,5-diketo system and elimination of the benzyloxy group, giving the dienone lactone **17**,[7a,c] mp 210–212 °C,[7d] in 47% yield. This material was identified by comparison[9] with authentic, naturally derived canrenone (**17**).[3b] Similarly lactone **14** was converted via **16**[7a] into the dienone lactone **18**,[6b,7a,b] mp 191–192 °C[7d] (65% yield), which was identified by comparison[9] with authentic 19-

(1) For a recent paper in the series on biomimetic polyene cyclizations, see: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513.
(2) Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J., *J. Am. Chem. Soc.* preceding communication in this issue.
(3) (a) Cella, J. A.; Brown, E. A.; Burtner, R. R. *J. Org. Chem.* **1959**, *24*, 743–748. (b) Cella, J. A.; Tweit, R. C. *Ibid.* **1959**, *24*, 1109–1110.
(4) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578–1591. The procedure employed was that of Gardner et al. (Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 1566–1570).
(5) Siddall, J. B.; Baddeley, G. V.; Edwards, J. A. *Chem. Ind.* (*London*) **1966**, 25–26.
(6) The product was purified by (a) chromatography on Florisil, (b) chromatography on silica gel.
(7) (a) The NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound. (c) The mass spectrum exhibited the correct molecular ion peak. (d) The melting point was determined on recrystallized material.
(8) Sturtz, G.; Yaouanc, J.-J.; Krausz, F.; Labeeuw, B. *Synthesis* **1980**, 289–291.
(9) The two substances were identical with respect to the following properties: $^1H$ NMR spectra, solution IR spectra, GC (coinjection) retention times.

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norcanrenone.[3b,10] Treatment of *dl*-canrenone (**17**) with thiolacetic acid[3b] provided, in 65% yield, *dl*-spironolactone (**19**),[6a,7a,c] mp 203–207 °C.[7d] This material was identified by comparison[9] with authentic spironolactone.[3b] Similarly *dl*-**18** was converted into *dl*-19-norspironolactone (**20**),[6b,7a,c] mp 209–219 °C (57% yield), which was identified by comparison[9] with authentic material.[3b] It is noteworthy that the 19-norsteroidal lactones are generally more potent as aldosterone blocking agents, but less readily accessible by partial synthesis, than the normal compounds.[3a]

**Acknowledgment.** We are indebted to the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. D.J.D. was the recipient of an NIH Postdoctoral Fellowship, and D.B. was supported by a fellowship from the Swiss National Science Foundation.

We also thank Dr. William F. Johns of the G. D. Searle Co. for arranging for us to receive the various authentic specimens of spironolactone and related substances that were used in this study.

**Registry No.** (±)-**5**, 81740-48-9; (±)-**6**, 81740-49-0; (±)-**7**, 81768-94-7; (±)-**8**, 81768-95-8; (±)-**9**, isomer 1, 81768-96-9; (±)-**9**, isomer 2, 81768-97-0; (±)-**10**, isomer 1, 81768-98-1; (±)-**10**, isomer 2, 81768-99-2; (±)-**11**, 81769-00-8; (±)-**12**, 81769-01-9; (±)-**13**, 81769-02-0; (±)-**14**, 81769-03-1; (±)-**15**, 81769-04-2; (±)-**16**, 81769-05-3; (±)-**17**, 81769-06-4; (±)-**18**, 81769-07-5; (±)-**19**, 81769-08-6; (±)-**20**, 81769-09-7.

(10) In work to be reported in detail elsewhere, the ketone **12**, on submission to the ozonolysis–cyclodehydration–elimination sequence (cf. **14** → **16** → **18**) afforded the dienedione (**18** with a 17-keto group in place of the lactone), which on selective hydrogenation of the 6,7 double bond was converted into *dl*-estr-4-ene-3,17-dione (Scott, J. W.; Saucy, G. *J. Org. Chem.* **1972**, *37*, 1652–1658), identified by comparison (ref 9) with authentic material.

## Total Synthesis of (−)-Domoic Acid. A Revision of the Original Structure

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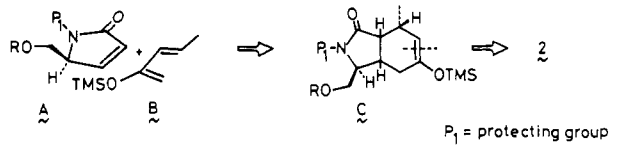
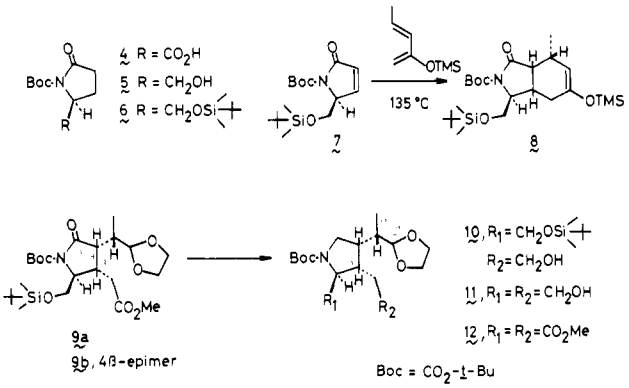
(−)-Kainic acid[1] (**1**) has attracted considerable interest in recent years owing to its potent neurotransmitting activity in the central nervous system.[2] The related structure **2**, with undefined stereochemistry at C-5′, was assigned[3a] to (−)-domoic acid[3b] isolated from the red algae *Chondria armata* Okamura (Rhodomelaceae) ("hanayanagi" or "domoi" in Japanese). Although domoic acid was known to exhibit similar neurobiological activities, only preliminary tests could be carried out owing to the extreme scarcity of sample available from marine sources; moreover, the algae itself has been depleted during the last decade. The synthesis of the proposed structure **2** was carried out for the aftermentioned reasons as well as to determine the C-5′ configuration. However, since neither of the synthetic C-5′ epimers corresponded to natural domoic acid, an X-ray crystallographic study of domoic acid was carried out, and this showed that the side chain had in fact the 1′*Z*,3′*E*,5′*R* stereochemistry (*ZER*)-**3**.[4] In the following we report the total synthesis of natural (−)-domoic acid (**3**) together with its *EER* and *EES* isomers **2**.

Scheme I




Scheme II




The synthesis was designed on the assumption that a [4 + 2] cycloaddition of **A** and **B** should lead to amide **C** for steric as well as electronic reasons[5] (Scheme I).

*N-tert*-Butoxycarbonyl-L-pyrroglutamic acid (**4**)[6] derived from L-glutamic acid was converted into the alcohol **5**:[7,8] (i) $ClCO_2Et/Et_3N/THF$, −10 °C; (ii) $NaBH_4$/90% EtOH, −10 °C. The silyl ether **6**[8] [oil, $[\alpha]^{25}_D$ −61° (*c* 1.1, $CHCl_3$)], obtained by reacting **5** with *tert*-butyldimethylsilyl chloride/DMF/imidazole, was converted into the unsaturated amide **7**[8] by the selenenylation–deselenenylation procedure [(i) LDA/THF/PhSeCl, −78 °C; (ii) $O_3/CH_2Cl_2$, −78 °C, NaOAc (powder), 0 °C] in 70% yield from **4**; mp 64–65 °C, $[\alpha]^{25}_D$ −176° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 7.26 (dd, *J* = 2, 7 Hz, 3-H), 6.12 (dd, *J* = 1.5, 7 Hz, 4-H), 4.60 (m, 2-H), 4.15 (dd, *J* = 4, 10 Hz, 2-$CH_2OSi$), 3.71 (dd, *J* = 7, 10 Hz, 2-$CH_2OSi$), 1.59 (s, *t*-BuO). The fact that no racemization had occurred during the last two steps was ascertained by hydrogenation of **7** to the starting material **6** ($H_2$/Pd–C, AcOEt), which exhibited the same specific rotation. Cycloaddtion of 2-(trimethylsilyl)oxy-1,3-pentadiene (prepared from *trans*-3-pentene-2-one/LDA/trimethylsilyl chloride, −78 °C; bp 150–153 °C)[9] to the pyrrolone **7** in toluene (135 °C, sealed tube, 3 days) proceeded stereospecifically to afford the single adduct **8**. The optical purity of **8** was checked by recovering unreacted starting material **7** after a 24-h reaction period and

(1) Structure: Murakami, S.; Takemoto, T.; Tei, Z.; Daigo, K. *J. Pharm. Soc. Jpn.* **1955**, *75*, 869. Synthesis: (a) Ueno, Y.; Tanaka, K.; Ueyanagi, J.; Nawa, H.; Sanno, Y.; Honjo, M.; Nakamori, R.; Sugawa, T.; Uchibayashi, M.; Osugi, K.; Tatsuoka, S. *Proc. Jpn. Acad.* **1957**, *33*, 53. (b) Oppolzer, W.; Andres, H. *Helv. Chim. Acta* **1979**, *62*, 2282.

(2) (a) Johnston, G. A. R.; Curtis, D. R.; Davis, J.; McCulloch, R. M. *Nature (London)* **1974**, *248*, 804. (b) Coyle, J. T.; Schwarz, R. *Ibid.* **1976**, *263*, 244. (c) McGeen, E. G.; McGeen, P. L. *Ibid.* **1976**, *263*, 517. (d) Shinozaki, K. "Kainic Acid as a Tool in Neurobiology"; Raven Press: New York, 1978.

(3) (a) Takemoto, T.; Daigo, K.; Kondo, Y.; Kondo, K. *J. Pharm. Soc. Jpn.* **1966**, *86*, 874. (b) Daigo, K. *Ibid.* **1959**, *79*, 350–365.

(4) Nomoto, K.; Iwashita, T.; Ohfune, Y.; Takemoto, T.; Daigo, K. to be submitted for publication.

(5) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1979**, *43*, 376.

(6) Schröder, E.; Krieger, K. *Justus Liebigs Ann. Chem.* **1964**, *673*, 196.

(7) Some racemization was encountered during the reduction of **4**, the resultant alcohol **5** having an $[\alpha]_D$ value of −57°. Removal of the racemate by recrystallization (acetone/hexane 1:20) afforded the optically pure **5** [70% conversion; mp 98–99 °C; $[\alpha]^{25}_D$ −63° (*c* 0.61, $CHCl_3$)], from the mother liquid. The conversion of **5** obtained in this manner to the starting material **4** with PDC/DMF led to optically pure material [$[\alpha]^{25}_D$ −35° (*c* 1.0, AcOH); (lit.[6] $[\alpha]^{25}_D$ −35° (AcOH))].

(8) Satisfactory spectroscopic data and elementary analyses were obtained.

(9) A regiospecific enolate formation of *trans*-3-penten-2-one has been reported: Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459.

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