# An Ascending Synthesis of Adrenalcorticosteroids. The Total Synthesis of (+)-Adrenosterone

Carolyn D. Dzierba, Kathleen S. Zandi, Thomas Möllers, and K. J. Shea*

*Department of Chemistry, University of California Irvine, California 92717-2025*

*Received January 24, 1996*

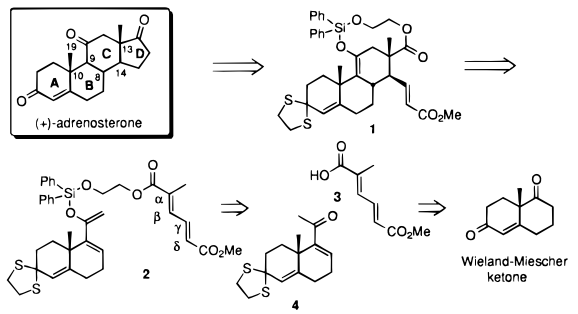
Pharmaceutically useful steroids may be obtained by total synthesis or by modification of readily available natural steroids.[1] The total synthesis route allows for enantiomer selection[2] as well as access to derivatives that may not be readily available by degradation or functional group conversions. We report a general strategy for the enantiospecific synthesis of the steroid skeleton. The approach is demonstrated by the synthesis of (+)-adrenosterone, an adrenalcorticosteroid.[3]

From a retrosynthetic perspective, an ascending strategy that appends the C-ring to an A, B fragment (AB → ABC → ABCD) utilizing a Diels−Alder construction represents a particularly efficient approach to this important class of natural products. The challenge entails control of regio-, stereo-, and $\pi$-facial selectivity in the C-ring-forming step. Often, the requirements for formation of the natural product countermand the intrinsic bias of the cycloaddition reaction. Despite earlier efforts, this strategy has not as yet been exploited in adrenalcorticoid synthesis.[4] Recent developments in controlling the stereoselectivity of the Diels−Alder reaction utilizing type 2 intramolecularity offered possible solutions to these problems.[5]

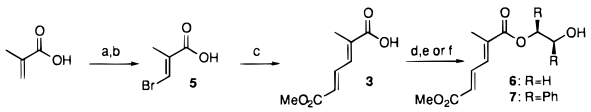
The strategy for the synthesis of (+)-adrenosterone is outlined in Scheme 1. A key step in the synthesis utilizes a temporarily union of diene and dienophile in a type 2 intramolecular Diels−Alder (T2IMDA) reaction to form the C-ring of the steroid.[5] The cycloaddition was designed to establish the four stereocenters in the BCD ring junctures ($C_8$, $C_9$, $C_{13}$, and $C_{14}$). In addition, the strategy has the potential for exploiting the $C_{19}$ methyl group to establish the correct absolute configuration at the new centers.

Dienophile **3** installs the $C_{18}$ methyl and the D-ring carbons. To circumvent the low reactivity of the $\alpha,\alpha,\beta$-trisubstituted dienophile, conjugation was extended through the carbomethoxy group (**3**, Scheme 1). Although this ploy introduced ambiguity in the chemoselectivity of the cycloaddition step (addition of the diene to the $\alpha,\beta$- *vs* $\gamma,\delta$-double bond), we relied upon the entropically more favorable $\alpha,\beta$-cycloaddition mode to deliver the steroidal skeleton. Following removal of the temporary tether and reduction of the $\alpha,\beta$−unsaturated ester, completion of the steroid relies upon Dieckmann cyclization/decarboxylation to form the D-ring.

**Scheme 1**




**Scheme 2**[a]




[a] (a) $Br_2$, *hν*, $CHCl_3$, 1 h; (b) aq NaOH, room temperature, 12 h, 87% (two steps); (c) methyl acrylate, cat. $Pd(OAc)_2$, $PPh_3$, $NEt_3$, $CH_3CN$, reflux, 24 h, 60%; (d) oxalyl chloride, DMF, $CH_2Cl_2$, reflux, 1 h; (e) ethylene glycol, $NEt_3$, $CH_2Cl_2$, 0 °C, 1 h, 97% (two steps); (f) (−)-hydrobenzoin, $NEt_3$, THF, room temperature, overnight, 70% (two steps).

The diene precursor **4** for the Diels−Alder reaction was prepared from (+)-Wieland−Miescher ketone by the procedure of Swaminathan *et al.*[6] Dienophile **6** was synthesized using a Heck coupling protocol, Scheme 2. Methacrylic acid was brominated in the presence of light followed by dehydrohalogenation with NaOH to give bromoacid **5** in 87% yield. Palladium-mediated coupling of **5** with methyl acrylate afforded diene acid **3** in 60% yield.[7] Conversion to the acid chloride with oxalyl chloride followed by quenching with excess ethylene glycol afforded glycol ester **6** in 97% yield.[8]

The diene and dienophile fragments were then joined by a temporary silyl acetal union, Scheme 3.[9,10] Enone **4** was kinetically deprotonated with KHMDS, trapped as the diphenylchlorosilyl dienol ether, and quenched with glycol ester **6** to give silyl acetal **2**. The silyl acetal was taken directly into the T2IMDA step without purification. The Diels−Alder reaction was carried out in toluene at 200 °C for 35 h to afford a 1:10 mixture of diastereomers (**8**:**9** respectively) in 90% yield from **4**. The tether was removed with $K_2CO_3$ in MeOH to give the corresponding ketones in a 1:10 ratio (**10**:**11** respectively) in 84% yield. The diastereomers were separated, and their absolute configurations were determined by X-ray crystallography.[11] The cycloadducts arose from exclusive tether *endo* attack of the dienophile with complete regiochemical control (1,3 *vs* 1,4 tether

(1) (a) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold Publishing Corp.: New York, 1959. (b) Akhrem, A. A.; Titov, Y. A. *Total Steroid Synthesis*; Plenum: New York, 1970.

(2) (a) Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732. (b) Mickus, D. E.; Levitt, D. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 359.

(3) For previous syntheses, see: (a) Velluz, L.; Nominé, G.; Mathieu, J.; Toromanoff, E.; Bertin, D.; Bucourt, R.; Tessier, J. *Compt. Rendu* **1960**, *250*, 1293. (b) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (c) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087. (d) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron* **1985**, *41*, 4667. (e) Kametani, T.; Matsumoto, H.; Honda, T.; Nagai, M.; Fukumoto, K. *Tetrahedron* **1981**, *37*, 2555. (f) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257.

(4) (a) Nazarov, I. N.; Gurvich, I. A. *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.* **1959**, 293. (b) Anner, G.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 1379.

(5) For examples of the type 2 intramolecular Diels−Alder reaction, see: (a) Shea, K. J.; Wise, S *J. Am. Chem. Soc.* **1978**, *100*, 6519. (b) Shea, K. J.; Beauchamp, P. S.; Lind, R. *J. Am. Chem. Soc.* **1980**, *102*, 4544. (c) Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *J. Am. Chem. Soc.* **1982**, *104*, 5708. (d) Shea, K. J.; Wada, E. *J. Am. Chem. Soc.* **1982**, *104*, 5715. (e) Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 419; *Angew. Chem. Suppl.* **1983**, 564−570. (f) Shea, K. J.; Burke, L. D.; England, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 860. (g) Shea, K. J.; Lease, T. G.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 8627. (h) Lease, T. G.; Shea, K. J. *J. Am. Chem. Soc.*, **1993**, *115*, 2248.

(6) (a) Swaminathan, S.; Newman, M. S. *Tetrahedron* **1958**, *2*, 88. (b) Ramakrishnan, V. T.; Ramachandran, S.; Venkataramani, P. S.; Swaminathan, S. *Tetrahedron* **1967**, *23*, 2453. (c) Darvesh, S.; Grant, A. S.; MaGee, D. I.; Valenta, Z. *Can. J. Chem.* **1989**, *67*, 2237. (d) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

(7) Heck, R. F. *Org. React.* **1982**, *27*, 345.

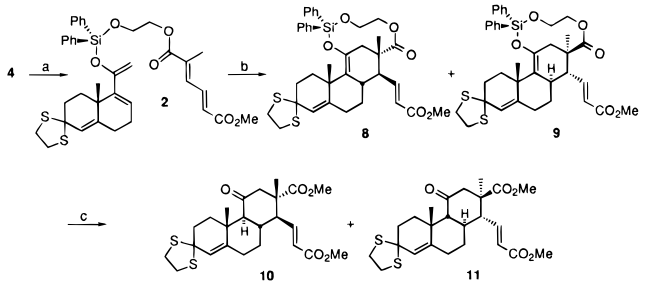
(8) This compound gave spectral ($^1H$, $^{13}C$, IR) and analytical (HRMS) data consistent with the assigned structure.

(9) (a) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885. (b) Shea, K. J.; Staab, A. J.; Zandi, K. S. *Tetrahedron Lett.* **1991**, *32*, 2715.

(10) (a) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585. (b) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, *33*, 4073. (c) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. (d) Posner, G. H.; Cho, C.-G.; Anjeh, T. E. N.; Johnson, N.; Horst, R. L.; Kobayashi, T.; Okano, T.; Tsugawa, N. *J. Org. Chem.* **1995**, *60*, 4617.

S0002-7863(96)00250-8 CCC: $12.00 

**Scheme 3**[a]



[a] (a) (i) KHMDS, THF, −78 °C, 2 h; (ii) $Ph_2SiCl_2$, $NEt_3$, 0 °C, 30 min; (iii) **6**, 0 °C → room temperature, overnight; (b) toluene, 200 °C, 35 h, 90% based on 50% conversion (two steps; 1:10 ratio of **8**:**9**); (c) $K_2CO_3$, MeOH, room temperature, 14 h, 87% (1:10 ratio of **10**:**11**).

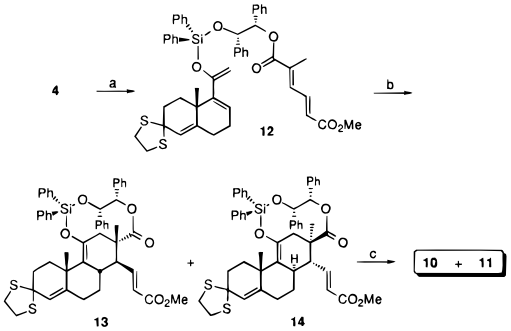
linkage). This regio- and stereochemical outcome is characteristic of the T2IMDA cycloaddition mode.[5,8] The reaction established the correct relative configuration at $C_8$, $C_{13}$, and $C_{14}$. However, the anticipated α-directing effect of the $C_{19}$ methyl group was not realized.[4] The major product **9** was derived from β-attack of the dienophile, a result that gives the nonnatural stereochemical relationship between $C_{10}$ and the $C_8$, $C_9$, $C_{13}$, and $C_{14}$ stereocenters.

Control of the π-facial selectivity in the cycloaddition step was the remaining hurdle in the synthesis.[12] Following inspection of molecular models, it was found that interactions between the phenyl groups on the silicon and an asymmetric center on the ethylene glycol fragment could possibly differentiate the π-faces of the T2IMDA cycloaddition step. To exploit this opportunity, (−)-hydrobenzoin was chosen as the source of asymmetry on the $C_2$ chain. Chiral hydrobenzoin dienophile **7** was prepared by quenching the acid chloride of **3** with (−)-hydrobenzoin[13] in 70% yield, Scheme 2.

Diels−Alder precursor **12** was prepared analogously to **2**, using dienophile **7**, Scheme 4. The triene, upon heating to 200 °C in toluene for 18 h, gave a 3:2 mixture of **13**:**14** in 90% yield (based on 45% conversion) from **4**. Subsequent treatment with $K_2CO_3$ in MeOH gave a 3:2 ratio of **10**:**11** in 80% yield. Gratifyingly, the (−)-hydrobenzoin auxiliary was found to reverse the π-facial selectivity of the ring closure. The major cycloadduct **8** arose from α-approach of the dienophile to give the correct stereochemical relationship between $C_{10}$ and the stereocenters at the BCD ring junctures.[14]

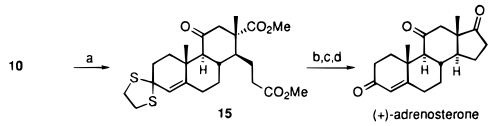
The remaining steps included reduction of the α,β-unsaturated double bond with Mg°/MeOH,[15] Scheme 5. It was desirable to interrupt this reaction after 70% conversion to avoid

**Scheme 4**[a]



[a] (a) (i) KHMDS, THF, −78 °C, 2 h; (ii) $Ph_2SiCl_2$, $NEt_3$, 0 °C, 30 min; (iii) **7**, DMAP, 0 °C → room temperature, overnight; (b) toluene, 200 °C, 18 h, 90% based on 45% conversion (two steps; 3:2 ratio of **13**:**14**); (c) $K_2CO_3$, MeOH, room temperature, 14 h, 84% (3:2 ratio of **10**:**11**).

**Scheme 5**[a]



[a] (a) (i) Mg°, MeOH, reflux, 2.5 h, 76% yield based on 70% conversion; (b) $^t$BuOK, benzene, reflux, 5 h; (c) (i) AcOH, HCl, $H_2O$, reflux, 1 h; (ii) 5% NaOH, MeOH, reflux, 1 h; (d) $Hg(ClO_4)_2$, THF, $H_2O$ room temperature, 1 h, 45% (three steps).

overreduction of the desired product. Dieckmann cyclization was induced upon heating with $^t$BuOK in benzene.[16] Saponification with acid and decarboxylation with NaOH provided the protected steroid. Deprotection of the dithiane with $Hg(ClO_4)_2$[17] yielded (+)-adrenosterone in 45% yield from **15**.

(+)-Adrenosterone was prepared in seven steps from enone **4**. A type 2 intramolecular Diels−Alder reaction was employed to control the regio- and stereochemistry of the cycloaddition. Temporary union of diene and dienophile by a chiral 1,2-diol provided control of the π-facial selectivity.

This strategy provides a general method for the construction of steroids. Since the stereocenters are set by the single stereocenter in the starting material, either enantiomer of the steroid can be prepared depending on the choice of enantiomer of Wieland−Miescher ketone.

**Acknowledgment.** We are grateful to the National Institutes of Health for financial support of this work. We thank Dr. Joseph Ziller for the X-ray crystallographic data.

**Supporting Information Available:** Crystallographic data and structures for compounds **10** and **11**; detailed experimental procedures as well as spectroscopic and analytical characterization of compounds **1**−**15** (63 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9602509

(11) (a) Compound **10** crystallizes from 8:2 hexanes/ethyl acetate in space group $P2_12_12_1$ with $a = 11.2595(4)$ Å, $b = 12.3209(6)$ Å, $c = 17.2587(14)$ Å, $V = 2394.3(2)$ Å$^3$, and $D_{calc} = 1.289$ mg/m$^3$ for $Z = 4$. Least-squares refinement of the model based on 2232 reflections ($F > 1.0\sigma(F)$) converged to a final $R_f = 3.6\%$. (b) Compound **11** crystallizes from 8:2 hexanes/ethyl acetate in space group $P2_1/c$ with $a = 6.8994(13)$ Å, $b = 19.501(2)$ Å, $c = 18.162(2)$ Å, $\beta = 99.354(9)^o$, $V = 2411.1(6)$ Å$^3$, and $D_{calc} = 1.280$ mg/m$^3$ for $Z = 4$. Least-squares refinement of the model based on 2682 reflections ($F > 2.0\sigma(F)$) converged to a final $R_f = 5.7\%$.

(12) Shea, K. J.; Gauthier, D. R., Jr. *Tetrahedron Lett.* **1994**, *35*, 7311.

(13) Wang, Z-M.; Sharpless, B. K. *J. Org. Chem.* **1994**, *59*, 8302.

(14) Ongoing studies have revealed that the π-facial selectivity of the cycloaddition step can be further improved by increasing the steric demands of the chiral auxiliary. Details of this work will be included in the full report of this work.

(15) (a)Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409. (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287.

(16) (a) Johnson, W. S.; Bannister, B.; Pappo, R. *J. Am. Chem. Soc.* **1956,** *78*, 6331. (b) Johnson, W. S.; Pappo, R.; Johns, W. F. *J. Am. Chem. Soc.* **1956,** *78*, 6339. (c) Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1940,** *62*, 824. (d) Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1939,** *61*, 974.

(17) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 203.