124.6, 119.7, 110.5, 89.2, 64.7, 56.2, 52.0, 41.7, 39.9, 36.2, 30.9, 29.7, 27.6; HRMS (EI) for $C_{17}H_{21}NO_4$ calcd 303.1470, found 303.1469.

(±)-Lycoramine (1). To a suspension of 10 mg of lithium aluminum hydride in 0.5 mL of freshly distilled THF was added a solution of 8 mg (0.03 mmol) of lactam 11 in 1 mL of THF. The reaction mixture was stirred at reflux 22 h under Ar, cooled, and quenched with 10% aqueous HCl solution. The aqueous solution was washed with EtOAc. Then NaOH pellets were added until the pH reached 10–12; the solution was saturated with sodium chloride and extracted with 3 × 10 mL of $CHCl_3$. The organic solution was washed with brine, dried over K_2CO_3, and concentrated to afford 6 mg (75%) of a pale yellow solid which was recrystallized from Et_2O: ^1H NMR ($CDCl_3$) 6.65 (d, 1 H, J = 8.0 Hz), 6.62 (d, 1 H, J = 8.0 Hz), 4.37 (br s, 1 H), 4.10 (br s, exch D_2O), 4.01 (d, 1 H, J = 15.3 Hz), 3.85 (s, 3 H), 3.70 (m, 1 H), 3.66 (d, 1 H, J = 15.3 Hz), 3.21 (t, 1 H, J = 13 Hz), 3.03 (d, 1 H, J = 14 Hz), 2.52 (d, 1 H, J = 15.3 Hz), 2.37 (s, 3 H), 2.01–1.65 (complex m, 9 H), 1.58 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 146.0, 144.2, 136.2, 125.8, 121.9, 110.8, 89.9, 65.3, 60.2, 55.8, 53.9, 46.7, 41.5, 31.5, 31.0, 27.6, 23.7; IR (CH_2Cl_2) 2934, 1626, 1503, 1441, 1415 cm^{-1}.

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Registry No. (±)-1, 18797-70-1; 2, 2973-58-2; 3, 137718-76-4; 4, 137718-77-5; (±)-5, 124549-69-5; (±)-6, 137718-78-6; (±)-7, 137718-79-7; (±)-7, 137718-83-3; (±)-8, 137718-80-0; (±)-9, 137718-81-1; (±)-10, 137718-82-2; (±)-11, 137742-02-0.

Supplementary Material Available: Tables of ^1H NMR decoupling data for compounds 7b and 9 and spectra for new compounds 3, 4, 6–11, synthetic lycoramine (1), and authentic (–)-lycoramine (33 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Photochemistry of Steroidal Ketones: Formation of an Exceptionally Stable Ketene by an α-Cleavage Reaction

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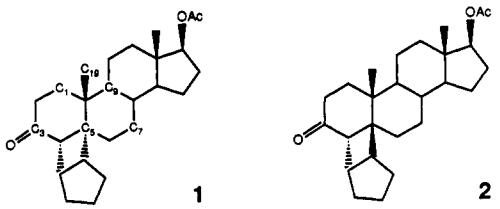
Upon irradiation, saturated cyclic ketones undergo preferential Norrish type I cleavage of the C–C bond between the carbonyl group and the more substituted α-carbon.[1] Exceptions to this general reactivity pattern are limited.[2-4] There is much evidence that the key intermediate is a triplet biradical,[5] which after a spin flip either recombines to give starting material or undergoes intramolecular hydrogen abstraction via a cyclic transition state.[6,7] Here we report that the isomeric testosterone acetate–cyclopentene adducts[8] 1 and 2 (Scheme I) not only undergo a Norrish type I cleavage toward the less substituted α-carbon in high yields, but also differ considerably in the fate of the intermediate 1,6-biradical.

Scheme I



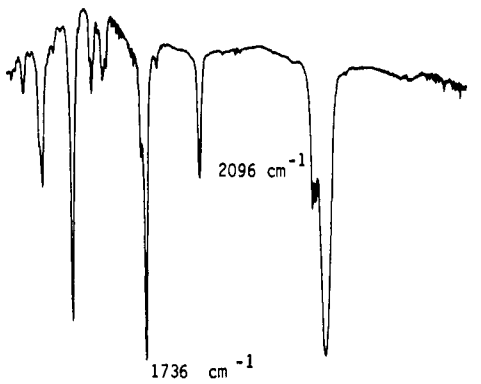


Figure 1. IR spectrum showing the presence of ketene 6 after irradiation of 2 in ethyl acetate for 45 min.

The cis-fused adduct 1 was irradiated in ethyl acetate. The major photoproduct (>80%) was identified as 4 (Scheme II) by ^1H NMR, ^{13}C NMR, IR, and GC–MS, indicating that cleavage toward the less substituted α-carbon atom had occurred.

The photoreactivity of 1 can be attributed to differences in the strength of the bonds between the carbonyl group and the adjacent carbon atoms, i.e., the higher s-character in the bond between the four-membered ring and the carbonyl carbon results in a stronger bond than the less substituted alkyl–acyl bond which preferably cleaves. A similar type of regioselective Norrish type I cleavage has been observed with *cis*- and *trans*-4,7,7-trimethylbicyclo-[4.1.0]heptan-3-one,[9] *cis*-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one,[2] and 22,29,30-trinorhopan-21-one.[4] In photo-CIDNP experiments, the proton of aldehyde 4 displays enhanced NMR absorption,[10] which further indicates that the triplet 1,6-biradical 3 (Scheme II) is indeed an inter-

(1) (a) Turro, N. J. *Modern Molecular Photochemistry*; Benjamin/Cummings: Menlo Park, 1978; pp 528–539. (b) Barltrop, J. A.; Coyle, J. D. *Excited States in Photochemistry*; Wiley: Chichester, 1978; pp 183–187. (c) Chapman, O. L.; Weiss, D. S. *Org. Photochem.* **1973**, *3*, 197.

(2) Fallis, A. G. *Can. J. Chem.* **1975**, *53*, 1657.

(3) Meinwald, J.; Schneider, P. A.; Thomas, A. F. *J. Am. Chem. Soc.* **1967**, *89*, 70.

(4) Trendel, J. M.; Albrecht, P. *Tetrahedron Lett.* **1984**, *25*, 1175.

(5) (a) Dalton, J. C.; Turro, N. J. *Ann. Rev. Phys. Chem.* **1970**, *94*, 9248. (b) Turro, N. J.; Dalton, J. C.; Dawes, R.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Schore, N. *Acc. Chem. Res.* **1972**, *5*, 92. (c) Closs, G. L.; Doubleday, C. E. *J. Am. Chem. Soc.* **1972**, *94*, 9248. (d) Kaptein, R.; Freeman, R.; Hill, H. D. *Chem. Phys. Lett.* **1974**, *26*, 104.

(6) Critch, S. C.; Fallis, A. G. *Can. J. Chem.* **1977**, *55*, 2845.

(7) Agosta, W. C.; Wolff, S. *J. Am. Chem. Soc.* **1976**, *98*, 4182.

(8) Schuster, D. I.; Kaprinidis, N. A.; Wink, D. J.; Dewan, J. C. *J. Org. Chem.* **1991**, *56*, 561.

(9) Wolff, S.; Venepalli, B. R.; George, C. F.; Agosta, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 6785.

(10) Kaprinidis, N. A.; Schuster, D. I.; Woning, J.; Gatlia, N. D.; Turro, N. J., unpublished results.

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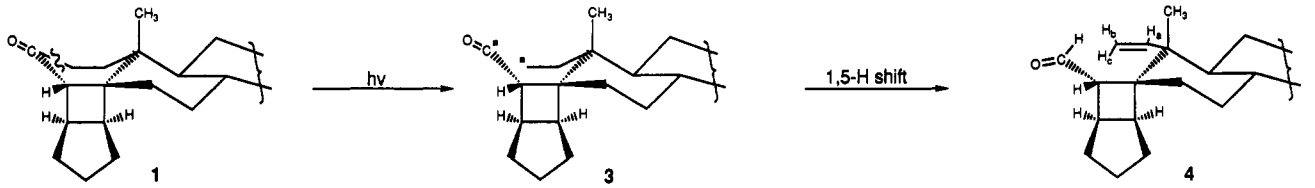
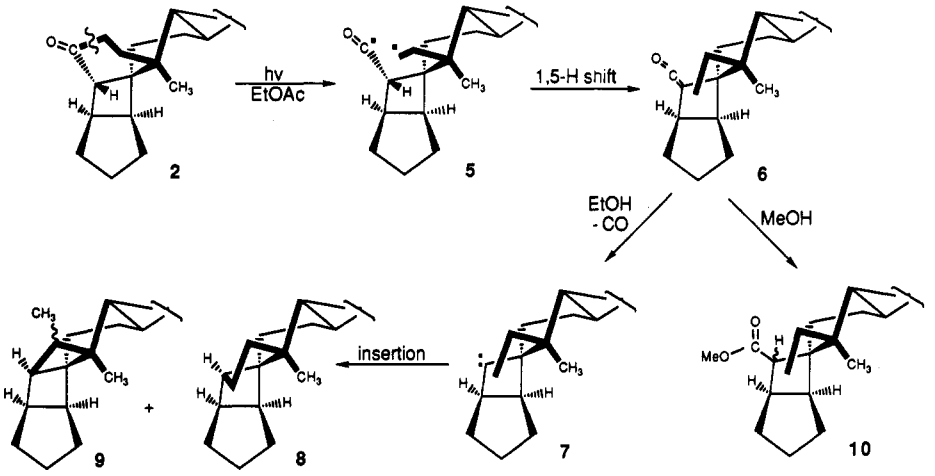
Scheme II



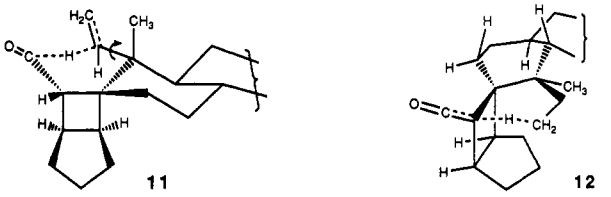
Scheme III



mediate in the photochemical cleavage of **1**.

Irradiation of the trans-fused adduct **2** in ethyl acetate resulted in the formation of a mixture of **8** and **9** in 85% yield (Scheme III). Consistent with the behavior of **1**, compound **2** also undergoes α-cleavage of the C–C bond at the less substituted side of the carbonyl group. However, in the case of **2**, the biradical intermediate **5** appears to undergo 1,5-H abstraction leading to ketene **6** rather than to an aldehyde isomeric with **4**. From repeated GC and GC–MS analyses it was established that, upon irradiation of **2**, ketene **6** is formed in significant quantity and, moreover, that it is stable enough that its EI mass spectrum can be obtained (see the Experimental Section). The most apparent feature in the latter is the occurrence of the molecular ion peak at m/z 398, while the absence of an $M^+ - 28$ peak indicates that thermal extrusion of CO from the molecular ion of **6** is insignificant. These MS data agree with those of ketene itself.[11] In accord with the thermal stability of ketene **6**, the FTIR spectrum of the reaction mixture from irradiation of **2** in ethyl acetate at room temperature (Figure 1) displays a band at 2096 cm^{-1} assigned as the C=O stretching vibration[12] of a heterocumulene moiety. This IR absorption gradually decays, presumably due to interaction of **6** with moisture or light. At room temperature and in the dark a degassed sample containing **6** proved to be indefinitely stable (vide infra). Under these conditions **6** could be trapped by addition of methanol to give ester **10** in high yield. The trapping of ketene **6** by methanol was inferred from the disappearance of its GC peak (retention time: ca. 10 min) and IR absorption at 2096 cm^{-1}, and concomitant appearance of the GC peak (rt ca. 11.3 min) due to **10**. Irradiation of **2** in methanol gave the same ester **10** as the major product (>85%). The structure of **10** was determined from its ^1H NMR, ^{13}C NMR, IR, and GC–MS data. Furher structural assignment regarding the stereochemistry at the carbon

Scheme IV



bearing the ester group is not possible, since the appropriate coupling constants could not be resolved in the complex 300-MHz ^1H NMR spectrum of **10**.

Upon exposure to light, ketene **6** appears to extrude CO. Thus, prolonged irradiation of **2** in ethyl acetate leads (presumably) to carbene **7** which undergoes intramolecular insertion to form a mixture of **8** and **9** (Scheme III). The same result is obtained when a degassed sample containing ketene **6** is allowed to stand for ca. 12 h under ambient illumination. GC–MS analysis of the mixture showed a molecular ion at m/z 370, consistent with the loss of CO from **6**. The two products are formed in a 4:1 ratio (GC). The ^1H NMR, ^{13}C NMR, and FTIR spectra of the mixture are compatible with formation of **8** and **9** as shown in Scheme III. The stereochemistry of the products shown in Scheme III is assigned based on the assumed mechanism for their formation. Further structural assignment is not possible at this time, since the mixture proved to be inseparable by GC and TLC. Entropy considerations for the insertion reaction favor formation of the five-membered ring (**8**), but the preferential formation of **9** from the highly reactive carbene[13] cannot be ruled out.

The difference in the reactivity of isomers **1** and **2** can be rationalized on the basis of their molecular structures.[8] In the 1,6-biradical deriving from **1**, the hydrogen at the α-carbon of the four-membered ring and the three-carbon fragment containing the radical center are at opposite faces of the four-membered ring. Consequently the transition

(11) (a) Long. F. A.; Friedman, L. *J. Am. Chem. Soc.* **1953**, *75*, 2837. (b) Vogt, J.; Williamson, A. D.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 3478 and references cited therein.

(12) Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 2449.

(13) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 173–176, 542–544 and references cited therein.

state required for abstraction of this hydrogen will be highly strained, favoring the alternative hydrogen abstraction from the acyl radical center to yield aldehyde 4 (transition state 11 in Scheme IV). In the 1,6-biradical derived from 2, the chain bearing the radical center and the hydrogen at the α-carbon of the four-membered ring have a cis relationship, favoring transition state 12 (Scheme IV) which results in formation of ketene 6.

Experimental Section

Reagents and solvents were obtained commercially and used as received. The testosterone acetate–cyclopentene adducts 1 and 2 were prepared according to ref 8. The mass spectra were taken on a HP 5988 mass spectrometer coupled to a HP 5890 GC, interfaced to a HP 9216 data processor. The GC was equipped with a 25 m × 0.25 mm dimethylsilicone capillary column and operated in the temperature-programmed mode (150–290 °C, heating rate: 32 °C/min). FTIR spectra were recorded on a Nicolet DX (10 scans, resolution: 4 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer, using TMS as the internal standard.

Irradiation of 1 and 2. Argon-purged solutions of 1 (0.012 M) in ethyl acetate and of 2 (0.012 M) in methanol were irradiated with a Hanovia 450-W high-pressure mercury lamp until conversion of the starting material was complete (GC–MS analysis). After irradiation, in each case, the solvent was removed under reduced pressure. The products 4 and 10, respectively, were purified by preparative TLC on Baker Si500F silica gel TLC plates, with hexane–ether (3:2 v/v) as the eluent.

4: ^1H NMR (300 MHz, $CDCl_3$) δ 9.93 (d, J = 3.6 Hz, 1 H, CHO), 6.20 (dd, J_{ab} = 11 Hz, J_{ac} = 17.7 Hz, 1 H, H_a) 5.19 (d, 1 H, H_b), 4.99 (1 H, d, H_c), 4.52 (t, 1 H, CHOAc), 2.1 (s, 3 H, AcO), 1.2 (s, 3 H, CH_3) 0.8 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.65, 171.10, 145.26, 115.12, 82.64, 60.58, 54.53, 50.97, 45.38, 44.96, 42.79, 40.10, 36.90, 35.20, 33.87, 30.98, 30.82, 28.37, 27.66, 27.52, 27.04, 23.29, 22.80, 21.50, 14.30, 12.16. IR ($CDCl_3$, cm^{-1}): 2930, 2830, 1735, 1725, 1400, 1350, 1250, 1000; MS m/z (rel intensity) 398 (M^+, 9), 355 (4), 331 (32), 330 (M^+ – 68 (cyclopentene), 27), 271 (18), 253 (26), 219 (19), 175 (22), 173 (23), 147 (52), 133 (43), 107 (61), 105 (72), 97 (67), 95 (48), 93 (85), 91 (89), 81 (81), 79 (96), 67 (100); HRMS calcd for $C_{26}H_{38}O_3$ 398.2821, found 398.2843.

10: ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (t, 1 H, C*H*OAc), 3.57 (s, 3 H, CH_3O), 2.2 (s, 3 H, CH_3), 0.84 (t, 3 H, CH_3CH_2), 0.77 (s, 3 H, CH_3), 0.76 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.00, 171.12, 82.84, 55.38, 51.62, 51.39, 50.68, 50.41, 47.28, 42.83, 42.50, 40.27, 37.66, 36.51, 35.05, 29.36, 29.13, 28.53, 28.23, 27.62, 27.51, 23.50, 21.51, 21.17, 12.29, 12.06, 11.88; IR (KBr, cm^{-1}) 2920, 1737, 1430, 1360, 1210, 913; MS m/z (rel intensity) 430 (M^+, 6), 362 (M^+ – 68 (cyclopentene), 32), 341 (31), 302 (18), 289 (19), 167 (52), 147 (41), 105 (49), 100 (51), 95 (51), 93 (78), 91 (68), 81 (89), 79 (78), 67 (100); HRMS calcd for $C_{27}H_{42}O_4$ 430.3083, found 430.3087.

Detection of Ketene 6. Ketene 6 was generated by irradiating an argon-purged solution of 2 (0.012 M) in ethyl acetate at ambient temperature for 45 min. GC–MS analysis of the reaction mixture showed the presence of ketene 6 (ca. 20%) along with unreacted starting material (ca. 54%) and traces of 8, 9, and an isomeric aldehyde analogous to 4. A few drops of the reaction mixture containing 6 were dispersed on a ZnSe plate. The solvent was allowed to evaporate and the FTIR spectrum shown in Figure 1 was acquired. The mass spectrum of 6 was obtained by GC–MS: MS m/z (rel intensity) 399 (6), 398 (M^+, 17), 302 (12), 175 (11), 164 (11), 161 (13) 159 (14), 147 (38), 105 (47), 91 (100), 79 (65), 67 (59). At this point, ketene 6 was trapped as ester 10 by adding 0.5 mL of methanol to the mixture. The trapping of the ketene by methanol was inferred from the disappearance of its GC peak (retention time: ca. 10 min), IR absorption at 2096 cm^{-1}, and concomitant appearance of the GC peak (rt ca. 11.3 min) due to 10.

Photolysis of 2 in Ethyl Acetate. Upon prolonged irradiation (2–5 h) of 2 in ethyl acetate, the intermediate ketene 6 extrudes CO, yielding compounds 8 and 9. The structures were assigned, assuming that the products are formed by intramolecular insertion of carbene 7. A mixture of the insertion products was separated from unreacted starting material by preparative TLC on Baker Si500F silica gel TLC plates, with hexane–ether (3:2 v/v) as the eluent. Attempts to separate 8 and 9 were unsuccessful, and therefore the ^1H and ^{13}C NMR data could not be unambiguously assigned. However, the presence of a triplet at δ 4.52 (1 H, CHOAc) and singlets at δ 2.2 (3 H, AcO), 0.98 (3 H, CH_3), and 0.84 (3 H, CH_3) in the ^1H NMR spectrum acquired from a 4:1 mixture of these products, indicated that both compounds retained the steroid carbon skeleton of the starting material 2. The presence of 9 in the mixture was supported by additional resonances (multiplet) observed in the region 0.72–0.77 ppm attributable to the newly formed methyl group (3 H, CH_3CH) in 9. The absence of the carbonyl moiety at the A ring is indicated by the absence of signals in the region 190–220 ppm of the ^{13}C NMR spectrum. The mass spectra of 8 and 9 were obtained by GC–MS analysis: MS m/z (rel intensity) for 8 371 (4), 370 (M^+, 14), 355 (5), 341 (26), 281 (14), 187 (17), 175 (18), 161 (20), 159 (39), 147 (36), 146 (23), 145 (39), 136 (69), 131 (47), 121 (43), 119 (55), 107 (77), 105 (82), 93 (77), 91 (100), 81 (70), 79 (90), 77 (48), 67 (62); for 9 371 (3), 370 (M^+, 10), 355 (5), 341 (22), 282 (9), 281 (10), 187 (21), 175 (22), 163 (15), 161 (18), 159 (33), 147 (46), 146 (27), 145 (32), 137 (34), 136 (67), 135 (58), 133 (35), 121 (38), 119 (44), 107 (73), 105 (71), 95 (42), 93 (77), 91 (90), 81 (67), 79 (100), 77 (43), 67 (66).

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Supplementary Material Available: ^1H NMR spectra of 4 and the mixture of 8 and 9 and the ^{13}C NMR spectrum of 10 (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis and Peptide Incorporation of (*S*)-α-Amino-(2,2′-bipyridine)-6-propanoic Acid†

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Recent approaches in the area of de novo protein synthesis have centered on the incorporation of metal cation binding sites within polypeptides as the basis for the assembly of new three-dimensional structures with defined structural, and potentially functional, properties.[1] A problem encountered in this quest, however, is that the number and diversity of *naturally* occurring metal-binding amino acids is limited, particularly when compared to the wide variety of synthetic ligands which are available for selective complexation of metal ions in aqueous media.[2] Thus, current objectives[3] involve an expansion of the repertoire of protein building blocks through the design and synthesis of *unnatural* metal-binding amino acids that would enhance metal cation selectivities as well as widen the range of metal coordination geometries beyond that which is currently available. We report herein the stereoselective synthesis of (*S*)-α-amino-(2,2′-bipyridine)-6-

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