dried over $MgSO_4$, and evaporated to afford 32 mg of crude **5**. Purification by flash chromatography (hexane, 1:3 ethyl acetate–hexane, 1:1 ethyl acetate–hexane, ethyl acetate) yielded 21 mg (72%) of **5**. A small sample was recrystallized from ether–petroleum ether to afford **5**: mp 124.5–125.5 °C; mp with authentic **5**[3] 123.5–125.0 °C (lit.[3] mp 124.0–125.8 °C); IR 3500–2100, 1720, 1700, 1465, 1445, 1430, 1395, 1370, 1330, 1315, 1265, 1250, 1240, 1200, 965, 935 cm^{-1} (IR of authentic **5**: 3500–2100, 1720–1690, 1465, 1445, 1430, 1395, 1370, 1330, 1315, 1265, 1250, 1240, 1200, 965, 940 cm^{-1}); ^1H NMR δ 0.79 (3 H, s), 1.1–2.5 (14 H, m) [^1H NMR of authentic **5**: δ 0.79 (3 H, s), 1.1–2.5 (14 H, m)]; ^{13}C NMR δ 16.9, 22.6, 23.1, 23.6, 39.2, 39.8, 40.2, 41.2, 42.6, 56.3, 180.9, 211.3 (^{13}C NMR of authentic **5**: δ 16.9, 22.6, 23.1, 23.6, 39.1, 39.8, 40.2, 41.2, 42.6, 56.3, 181.1, 211.3).

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Registry No. (±)-**3**, 113999-08-9; **4**, 113999-18-1; (±)-**5**, 42246-08-2; (±)-**6**, 3287-59-0; **8**, 1193-18-6; **9**, 42201-43-4; **10**, 113999-09-0; **11**, 102147-75-1; **12**, 113998-32-6; (±)-**13**, 113999-10-3; (±)-**17**, 113999-11-4; (±)-**18** (isomer 1), 113999-12-5; (±)-**18** (isomer 2), 113999-19-2; (±)-**19**, 113999-13-6; (±)-**20**, 113999-14-7; (±)-**21**, 113999-15-8; (±)-**25**, 113999-16-9; (±)-**27**, 113999-17-0; diethyl allylmalonate, 2049-80-1.

Synthesis of (±)-7-Epivaleranone and (±)-Valeranone

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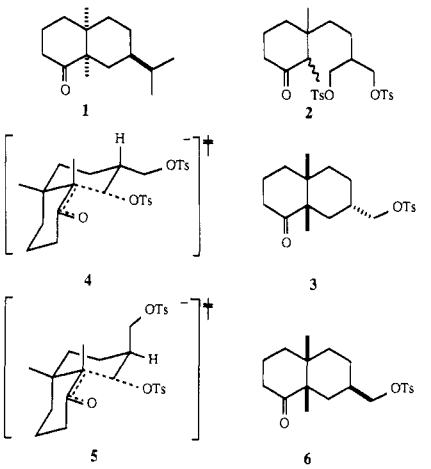
The cyclization of ditosylate **2** was investigated as a possible diastereoselective route to compounds like valeranone (**1**) which possess a C7 substituent trans to the angular methyl groups. However, cyclization of **2** (which was prepared via reaction of **9** with **7** to afford **11**, followed by reaction with lithium dimethylcuprate, hydrolysis, and tosylation) produced exclusively the 7β-substituted **6**, which was identified by its conversion to (±)-7-epivaleranone (**13**). A synthesis of (±)-**1** was achieved via elimination product **20** derived from **6**. This synthesis proceeded analogously to the conversion of **6** to **13**, involving the sequence **20** → **21** → **22** → **23** → **25** → **1**.

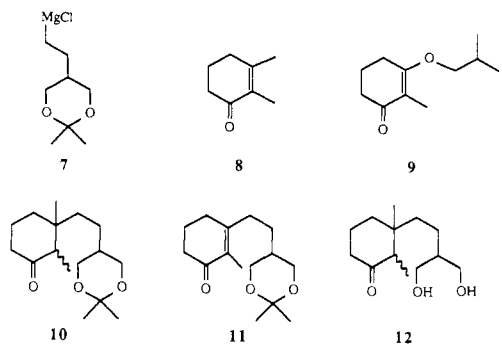
The natural product (−)-valeranone (**1**) is unusual in that its isoprene units are not connected in the "head-to-tail" fashion found in the biogenetic progenitor of sesquiterpenes, farnesyl pyrophosphate. Initial confusion about the structure and stereochemistry of valeranone was corrected in the early 1960s[1] and the structural assignment was confirmed shortly thereafter by a synthesis of (±)-valeranone by Marshall.[2] There have been several subsequent syntheses of the valeranone structure,[3-5] among which Wenkert's short synthesis of (−)-valeranone stands out for its elegant solution to the difficult problem of introducing the second angular methyl group.[6]

Our hope was that a stereoselective synthesis of (±)-valeranone could be achieved via diastereoselective cyclization of ditosylate **2** to form **3** having the C7 (tosyloxy)methyl group trans to the angular methyl groups, as is the isopropyl group in **1**. The opposite stereochemical result had been obtained in the cyclization of the ditosylate lacking the methyl group α to the carbonyl group, as described in the preceding paper.[7] Nonetheless, our predisposition to consider transition states with chair-like conformations encouraged us to predict that the presence of that additional methyl group would favor **4**, leading to **3**, over **5**, which would lead to **6**, owing to the severe 1,3-diaxial interaction in the latter transition state. If **3** were



indeed obtained, subsequent elaboration to valeranone (**1**) would be expected to be straightforward.

The first approach to synthesis of intermediate ditosylate **2** involved conjugate addition of the Grignard reagent **7**, which had been used in the synthesis of (±)-β-eudesmol,[7] to 2,3-dimethylcyclohex-2-en-1-one (**8**), which was readily prepared from **9**[8] by Jung's procedure.[9] However, cop-



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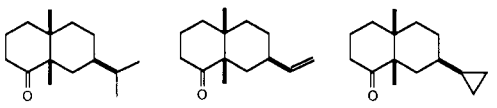
0022-3263/88/1953-2560$01.50/0

per-catalyzed addition of **7** to **8** afforded only 23% of the desired **10**. This result is consistent with literature reports that low yields are obtained in such reactions when the enone bears an α substituent.[10,11] Although more effective conjugate addition would be expected by use of the corresponding lithium dialkylcuprate,[11] such an approach would have wasted 1 equiv of the nontrivial alkylating agent, so the alternate approach of adding **7** to **9** was undertaken.[12,13] The expected product **11** could then be treated with lithium dimethylcuprate to afford **10**.

Addition of **7** to **9** proceeded smoothly and afforded 79% of **11**, after a procedure was developed to remove unreacted **9** by its selective hydrolysis with saturated aqueous ammonium chloride. Initially, reaction of **11** with lithium dimethylcuprate afforded about equal amounts of the desired **10** and what appeared to be 1,2-addition product, but use of trimethylsilyl chloride, as described by Corey,[14] led to a greatly improved ratio of conjugate to direct addition. The crude product was hydrolyzed with acid to afford **12** as a mixture of C2 stereoisomers in 77% yield. Diol **12** was then converted to ditosylate **2** in 96% yield by the procedure of McAuley.[15]

Cyclization of **2** was effected by use of sodium *tert*-pentoxide in benzene[12] to afford 61% (80% based on consumed **2**) of a single crystalline bicyclic product. Since the cyclization can be assumed to give a product with a cis ring fusion,[12] the structure of the bicyclic material was either the hoped-for **3** or its C7 epimer **6**. Based on optimism that the product was indeed **3**, it was decided to carry it through transformations intended to lead to (±)-valeranone (**1**). However, these efforts afforded instead (±)-7-epivaleranone (**13**), disappointingly establishing the structure of the cyclization product as **6**.

The strategy adopted for conversion of the cyclization product to the valeranone skeleton envisioned transforming **6** into homologated alkene **14**, followed by cyclopropanation to **15** and hydrogenolysis of the cyclopropane ring.[16] The first method tried for the conversion of **6** to **14** was that of Entwistle and Johnstone,[17] involving displacement of tosylate with dimsyl anion followed by pyrolytic elimination of dimethyl sulfoxide. However, the displacement by dimsyl anion proceeded in poor yield, and the pyrolytic elimination also proved troublesome. Several variations of this method were attempted but were also unpromising, so the following alternate approach was adopted.



13 14 15

Tosylate **6** was readily converted to alcohol **16** in 83% yield by treatment successively with sodium acetate in dimethylformamide and potassium carbonate in aqueous methanol. Oxidation of **16** with pyridinium chlorochromate[18] (PCC) then gave 88% of keto aldehyde **17**. Since PCC is known to effect oxidation of alcohols without causing enolization of the product carbonyl compounds,[19] we were confident that epimerization at C7 had not occurred, a conclusion confirmed by the results described below. For some reason, aldehyde **17** was unusually labile to oxidation and was completely converted to the corresponding keto acid upon exposure to air for just several hours. Wittig reaction of **17** with 1 equiv or an excess of triphenylphosphonium methylide then furnished alkene **14** in 90% yield.

The next step, cyclopropanation of alkene **14** to form **15** proved to be challenging, and considerable difficulty was encountered in developing successful conditions for a Simmons–Smith reaction[20] on the small amounts of **14** which were available. Various methods for activating zinc were explored, including preparation of a zinc–copper couple,[21] preparation of a zinc–silver couple,[22] and ultrasound irradiation.[23] Studies on model compounds revealed a sensitivity to concentration of cyclopropanating reagent, which could not be lowered as the scale of the reaction was reduced without severely lowering the yield of cyclopropane. Eventually, an effective combination of known methods was discovered in which a zinc–silver couple and ultrasound irradiation are used to form the cyclopropanating reagent. Under these conditions, **14** was converted to **15** in 68% yield.

Hydrogenolysis of the cyclopropane ring according to Oppolzer's procedure[16] proceeded uneventfully to afford 90% of what, unhappily, proved to be (±)-7-epivaleranone (**13**) rather than (±)-valeranone (**1**). Comparison of the IR and ^{1}H NMR spectra of our product with those of authentic (−)-valeranone,[6] kindly furnished by Professor E. Wenkert, left no question that we had **13** in hand rather than **1**. For example, the singlets for the angular methyl groups in **1** appear at δ 0.81 and 1.06, whereas those in **13** are at δ 0.97 and 1.05.[24]

The methyl singlet at δ 0.81 in valeranone has been implicitly assigned to the C10 methyl group,[25] and this relatively high field chemical shift is consistent with the shielding effect the carbonyl group would have on a methyl group axially oriented to the ring containing that carbonyl group,[26] indicating that valeranone exists, as would be expected, in conformation **18** with the C7 isopropyl group equatorial. Conversely, the relatively deshielded C10 methyl group of 7-epivaleranone (**13**) is consistent with its being equatorial to the ring containing the carbonyl group,[26] indicating that **13** adopts conformation **19**, again as would be expected.

Although a stereoselective route to (±)-valeranone (**1**) obviously had not been achieved, it was still hoped to effect a synthesis of that natural product. A reasonable means to that end was suggested by the fact that the cyclization of **2** to **6** produced 20% of keto alkene **20** when that reaction was carried out in a mixture of tetrahydrofuran and

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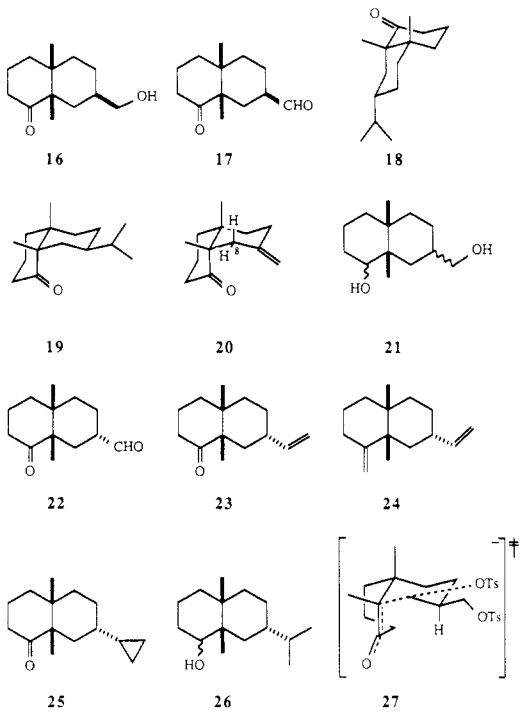
hexamethylphosphoramide instead of benzene. If a good yield of **20** could be obtained, its exocyclic methylene group



might well be convertible to a 7α substituent which could be transformed to the isopropyl group of **1**. When **2** was treated with excess potassium *tert*-butoxide in *tert*-butyl alcohol, **20** was indeed the major product (68%), along with 21% of **6**. The fact that the ^{1}H NMR spectrum of **20** showed doublets at δ 1.75 and 2.76 for the two protons on C8 suggests that **20** exists in the conformation shown, because only in that conformation is a C8 proton, the α H, situated in the deshielding cone of the carbonyl group, accounting for the doublet at the unusually low field of δ 2.76.

It was hoped that oxidative hydroboration of **20** might lead selectively to a compound with a 7α hydroxymethyl group, but the conformational mobility of the *cis*-decalin structure and the fact that the carbonyl group of **20** would presumably be hydroborated first,[27] made any prediction of stereochemical outcome treacherous. In the event, essentially no stereoselectivity was observed when **20** was treated with an excess of 9-BBN followed by oxidative workup. A mixture of all four possible diols **21** was obtained, with no single isomer dominating. Two of these diols were identified as having a 7β hydroxymethyl substituent by PCC oxidation to the familiar keto aldehyde **17**.

A third isomer, obtained in 26% yield from the oxidative hydroboration, provided a different keto aldehyde upon PCC oxidation, and this compound was confirmed as **22** by its conversion to (±)-valeranone (**1**) through the same sequence used to convert **17** to **13**. Wittig reaction of **22** afforded 95% of **23**, but in this case, as opposed to the Wittig reaction of **17**, use of excess reagent had to be avoided or some diene **24** was produced. Simmons–Smith reaction of **23** by the procedure worked out for **14** afforded 62% of **25**. The hydrogenolysis of **25**, like the Wittig reaction of **22**, gave different results than were obtained in the 7-epivaleranone series, for hydrogenation of **25** over platinum oxide in acetic acid[16] effected reduction of the carbonyl group as well as cleavage of the cyclopropane ring, affording a 9:1 mixture of alcohols **26** in quantitative yield. Oxidation of the major isomer with PCC then finally afforded (±)-valeranone (**1**) in 84% yield from **25**. This synthetic (±)-valeranone had IR and ^{1}H NMR spectra identical with those of natural (−)-valeranone.[6]

The isolation of **6**, with a 7β substituent, as the *only* product from the key cyclization of **2** was unexpected, and a convincing rationalization of this diastereoselectivity would be useful in predicting the course of other intramolecular alkylations. Unfortunately, just as in the case discussed in the preceding paper,[7] we have not been able to generate an unequivocal explanation of this stereochemical result. As Evans noted for an analogous case,[28] there would appear to be little difference in energy between the conformers of the enolate anion of **2** which have the ditosylate side chain pseudoaxial or pseudoequatorial, respectively, and one must consider relatively advanced transition states such as **4** and **5** in order to perceive any potential differences in stereochemical favorability. In the present case, the exclusive isolation of **6** requires that the reaction involves either a transition state like **5** or one like **27**, involving equatorial alkylation of a boat-like conformation. Since there is indeed a serious 1,3-diaxial interaction in **5**, **27** might seem preferable. However, the possibility that there is a sufficiently large eclipsing interaction in **4** to make that transition state less favorable than **5**, as discussed for the closely related reaction in the preceding paper,[7] cannot be ruled out.

Experimental Section

All general information concerning experimental procedures is exactly the same as that given in the preceding paper.[7]

3-Isobutoxy-2-methylcyclohex-2-en-1-one (9). The method of Eschenmoser[8] was used to afford 93% of **9**: bp 109–111 °C (1.25 mm) [Lit.[9] bp 82 °C (0.06 mm)].

2,3-Dimethylcyclohex-2-en-1-one (8). The procedure of Jung[9] was used to convert **9** in 82% yield to **8**: bp 105–107 °C (20 mm) [lit.[9] bp 65 °C (10 mm)].

3-[2-(2,2-Dimethyl-1,3-dioxan-5-yl)ethyl]-2,3-dimethylcyclohexanone (10). A solution of 3.10 g (17.4 mmol) of 5-(2-chloroethyl)-2,2-dimethyl-1,3-dioxane[7] in 7 mL of dry THF and 0.05 mL of 1,2-dibromoethane were added to 1.27 g of magnesium turnings under N_2. The reaction mixture was gently heated in order to initiate formation of Grignard reagent **7**. The exothermic reaction subsided, and the mixture was stirred for 45 min at room temperature. The mixture was cooled to −78 °C and a solution of 1.19 g (5.80 mmol) of cuprous bromide–dimethyl sulfide complex in 10 mL of dry dimethyl sulfide was added via syringe. The mixture was stirred for 1.5 h and a solution of 1.44 g (11.6 mmol) of **8** in 22 mL of dry ether was added over 20 min. The reaction was monitored by IR spectroscopy. After 21 h at −78 °C, the mixture was allowed to warm to 0 °C over 2 h. The mixture was stirred at 0 °C for 1 h, warmed to room temperature, and stirred for 30 min. Only a minor absorption corresponding to a saturated carbonyl group was observed in the IR. The reaction mixture was quenched with 40 mL of saturated aqueous NH_4Cl and stirred for 30 min. The mixture was filtered through glass wool and the organic layer was removed. The organic layer was washed with 50 mL of water and 50 mL of $NaHCO_3$. The combined aqueous layers were extracted with ether (2 × 50 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated. Distillation followed by flash chromatography (hexane, 1:9 ethyl acetate–hexane, 1:4 ethyl acetate–hexane, 1:1 ethyl acetate–hexane) provided 0.728 g (23%) of **10** as a colorless oil: bp 160–165 °C (0.75 mm); IR 1715, 1460, 1385, 1260, 1200, 1165, 1075, 840 cm^{-1}; ^{1}H NMR δ 0.75 (1 H, s) 0.90 (1 H, d), 1.00 (2 H, s), 1.03 (2 H, d), 1.42 (6 H, s), 1.10–2.10 (9 H, m), 2.20–2.50 (3 H, m), 3.30–4.10 (4 H, m); MS, *m/e* 187 ($M^+ - CH_3$), 129, 109, 69, 59 (base), 43;

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TLC R_f 0.47 (1:1 ethyl acetate–hexane). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.43; H, 10.31.

3-[2-(2,2-Dimethyl-1,3-dioxan-5-yl)ethyl]-2-methylcyclohex-2-en-1-one (11). In an adaptation of Conia's procedure,[12] a flame-dried flask containing 2.58 g (106 mmol) of magnesium turnings under N_2 was charged with 5 mL of dry ether. Spontaneous reflux occurred upon addition of 0.10 mL of 1,2-dibromoethane. When the initial exothermic reaction subsided, a solution of 6.32 g (35.4 mmol) of 5-(2-chloroethyl)-2,2-dimethyl-1,3-dioxane[7] in 15 mL of dry THF was added over 10 min. An additional 0.10 mL of 1,2-dibromoethane was added and the mixture was heated at reflux for 30 min. Then, a solution of 3.22 g (17.7 mmol) of **9** in 15 mL of dry THF was added in a dropwise manner via syringe and reflux was maintained for 2.5 h. After the mixture cooled to room temperature, the liquid phase was decanted from the excess magnesium turnings. Saturated aqueous NH_4Cl (25 mL) was added to the decanted liquid and the organic layer was separated. The aqueous layer was extracted with ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 7.44 g of clear oil. Flash chromatography (hexane, 1:3 ethyl acetate–hexane, 1:1 ethyl acetate–hexane, ethyl acetate) afforded 3.52 g (79%) of **11** as a clear oil: IR 1670, 1635, 1460, 1380, 1260, 1200, 1160, 1075, 1040, 835; ^{1}H NMR δ 1.42 (6 H, s), 1.50–2.50 (14 H, m), 3.40–4.15 (4 H, m); ^{13}C NMR δ 10.5, 21.4, 22.4, 26.3, 26.4, 30.7, 32.3, 34.4, 37.6, 64.4, 97.9, 131.0, 157.8, 199.3; MS, *m/e* 252 (M^+), 237 ($M^+ - CH_3$), 194, 159, 149, 137, 136, 135, 133, 124 (base), 119, 108, 107, 95, 93, 79, 67, 55. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 70.98; H, 9.60.

2,3-Dimethyl-3-[3,3-bis(hydroxymethyl)propyl]cyclohexanone (12). In a modification of Corey's method,[14] a suspension of 5.72 g (27.8 mmol) of cuprous bromide–dimethyl sulfide complex in 15 mL of dry THF under N_2 was cooled to 0 °C and treated with 49 mL (56 mmol, 1.14 M in ether) of methyllithium. The initial, bright yellow precipitate gave way to a clear solution on complete addition of the methyllithium. The solution was stirred for 15 min and then cooled to −78 °C in a dry ice–isopropyl alcohol bath. To the cooled mixture was added 9 mL (70 mmol) of TMSCl. After 5 min, a solution of 3.52 g (13.9 mmol) of **11** in 15 mL of dry THF was added dropwise via syringe at such a rate that the temperature could be maintained below −65 °C. The mixture was stirred for 2.5 h at −78 °C and allowed to warm to room temperature over 0.5 h. After being stirred for an additional 1.5 h, the mixture, which contained a thick yellow precipitate, was slowly poured into 150 mL of saturated aqueous NH_4Cl with rapid stirring that was continued for 15 min. The organic layer was removed and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with 50 mL of brine, dried over Na_2SO_4, and evaporated to give 3.32 g of clear oil.

Without purification, this oil was dissolved in 24 mL of THF, cooled in an ice–water bath, and treated with 8 mL of 1 M HCl, and the resulting solution was allowed to warm to room temperature and stirred overnight. Then, 2 g of solid $NaHCO_3$ was added and the organic layer was removed. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were dried over Na_2SO_4 and evaporated to give 3.06 g of clear oil. Flash chromatography (ethyl acetate) afforded 2.45 g (77%) of **12** as a colorless, viscous oil that was a 1:1 mixture of diastereomers: IR 3400, 1710, 1455, 1375, 1240, 1040 cm^{-1}; ^{1}H NMR δ 0.75 (1.5 H, s), 0.90 (1.5 H, d), 1.00 (1.5 H, s), 1.02 (1.5 H, d), 1.10–2.10 (9 H, m), 2.20–2.60 (3 H, m), 2.98 (2 H, s), 3.60–3.85 (4 H, m); HRMS, *m/e* 228.1742 (calcd for $C_{13}H_{24}O_3$ 228.1726).

2,3-Dimethyl-3-[3,3-bis[(tosyloxy)methyl]propyl]cyclohexanone (2). According to the procedure of McAuley,[15] 20 mL of dry CH_2Cl_2 and 20 mL of triethylamine were added to 2.40 g (10.5 mmol) of **12**. The mixture was cooled to −15 °C in an ice–salt bath. A solution of 4.20 g (22.0 mmol) of *p*-toluenesulfonyl chloride in 20 mL of dry CH_2Cl_2 was added over 10 min. The mixture was stored at −20 °C for 48 h and then poured into 100 mL of ice–water. The organic layer was separated and washed with 0.5 M HCl (2 × 60 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 30 mL of $NaHCO_3$, dried over Na_2SO_4, and evaporated to give 6.14 g of crude **2**. Flash chromatography (hexane, 1:3 ether–hexane, 1:1 ether–hexane) afforded 5.43 g (96%) of **2** as a 2:1 mixture of diastereomers: mp 94–99 °C; IR 1705, 1595, 1360, 1185, 1175, 960, 950, 935, 865, 830, 815, 665 cm^{-1}; ^{1}H NMR δ 0.67 (1 H, s), 0.80 (1 H, d), 0.90 (2 H, s), 0.92 (2 H, d), 1.0–2.40 (12 H, m), 2.50 (6 H, s), 3.90–4.10 (4 H, dd), 7.67 (8 H, q); MS, *m/e* 536 (M^+). Anal. Calcd for $C_{27}H_{36}O_7S_2$: C, 60.42; H, 6.76; S, 11.95. Found: C, 60.18; H, 6.83; S, 11.78.

2,3,4,5,6,7,8,9-Octahydro-9β,10β-dimethyl-7β-[(tosyloxy)methyl]-1(10*H*)-naphthalenone (6). In a modification of Conia's procedure,[14] 0.628 g (5.70 mmol) of sodium *tert*-pentoxide was dissolved in 10 mL of dry benzene under N_2. The mixture was cooled in an ice–water bath throughout the dropwise addition of a solution of 1.53 g (2.85 mmol) of **2** in 5 mL of dry benzene. The mixture was allowed to warm to room temperature, stirred for 3.5 h, and poured into 20 mL of saturated aqueous NH_4Cl, and the resulting precipitate was dissolved by the addition of 10 mL of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, and evaporated to give 0.902 g of yellow oil. Flash chromatography (1:3 ethyl acetate–hexane) provided 0.130 g (24%) of **2** and 0.638 g (61%) of **6** as a white solid, mp 65–67 °C. An analytical sample was obtained by recrystallization from ether–petroleum ether: mp 69.5–70.5 °C; IR 1700, 1599, 1375, 1360, 1185, 1175, 970, 940, 840, 810, 665 cm^{-1}; ^{1}H NMR δ 0.95 (3 H, s), 1.02 (3 H, s), 1.05–2.10 (13 H, m), 2.43 (3 H, s), 3.70–3.90 (2 H, m), 7.55 (4 H, q); ^{13}C NMR δ 20.7, 21.6, 22.4, 23.2, 24.2, 32.1, 33.1, 34.2, 34.7, 37.4, 38.8, 51.7, 75.0, 127.8, 129.7, 132.9, 144.5, 215.6. Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H, 7.74; S, 8.80. Found: C, 65.82; H, 7.81; S, 8.83.

2,3,4,5,6,7,8,9-Octahydro-7β-(hydroxymethyl)-9β,10β-dimethyl-1(10*H*)-naphthalenone (16). A solution of 500 mg (1.37 mmol) of **6** in 5.5 mL of dry DMF under N_2 was treated with 225 mg (2.74 mmol) of anhydrous sodium acetate. The mixture was heated at 120 °C for 2 h and then cooled to room temperature. The mixture was diluted with 25 mL of ether and washed with water (3 × 10 mL). The combined aqueous layers were extracted with ether (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give 467 mg of a colorless oil: IR 1735, 1705, 1240 cm^{-1}; TLC R_f 0.59 (1:1 ethyl acetate–hexane). Without purification, this oil was dissolved in 98% aqueous methyl alcohol and treated with a catalytic amount of K_2CO_3. The mixture was stirred for 3 h and the solvent was evaporated. The residue was taken up in ether, dried over anhydrous K_2CO_3, filtered, and evaporated to give 0.346 g of crude **16**. Flash chromatography afforded 238 mg (83%) of **16** as a colorless liquid: IR 3420, 1705, 1470, 1445, 1430, 1385, 1370, 1320, 1250, 1150, 1080, 1040, 1015 cm^{-1}; ^{1}H NMR δ 0.97 (3 H, s), 1.04 (3 H, s), 1.05–2.60 (14 H, m), 3.40–3.70 (2 H, m); ^{13}C NMR δ 20.8, 22.7, 23.6, 24.7, 33.0, 34.8, 35.0, 36.5, 37.7, 39.2, 52.0, 68.5, 216.1; MS, *m/e* 192 ($M^+ - H_2O$), 177, 149 (base), 134, 107, 93; HRMS, *m/e* 210.1620 (calcd for $C_{13}H_{22}O_2$ 210.1626).

2,3,4,5,6,7,8,9-Octahydro-7β-formyl-9β,10β-dimethyl-1-(10*H*)-naphthalenone (17). According to the method of Corey,[18] a solution of 177 mg (0.840 mmol) of **16** in 2 mL of dry CH_2Cl_2 was added rapidly to a suspension of 272 mg (1.26 mmol) of PCC in 2 mL of dry CH_2Cl_2 at room temperature. After 2 h, the brown mixture was diluted with 4 mL of ether. The liquid phase was decanted and filtered through silica gel. The black tar was triturated with ether (3 × 2 mL). The ether extracts were filtered through silica gel and the combined filtrates were evaporated to give 154 mg (88%) of **17** as a pale yellow liquid that was nearly homogeneous by TLC: IR 2730, 1730, 1710, 1475, 1455, 1435, 1390, 1375, 1325, 1265, 1155, 1060, 1035, 960 cm^{-1}; ^{1}H NMR δ 0.98 (3 H, s), 1.11 (3 H, s), 1.00–2.05 (9 H, m), 2.23 (2 H, d), 2.48–2.64 (2 H, m), 9.62 (1 H, s); ^{13}C NMR δ 20.7, 21.1, 22.3, 23.0, 29.2, 33.9, 34.7, 37.4, 39.2, 46.4, 51.4, 204.3, 215.5; TLC R_f 0.33 (1:3 ethyl acetate–hexane); HRMS, *m/e* 208.1459 (calcd for $C_{13}H_{20}O_2$ 208.1464).

2,3,4,5,6,7,8,9-Octahydro-7β-vinyl-9β,10β-dimethyl-1-(10*H*)-naphthalenone (14). As in the procedure by Conia,[29] 298 mg (0.834 mmol) of methyltriphenylphosphonium bromide was suspended in 2 mL of dry benzene under N_2. To the suspension was added 88 mg (0.800 mmol) of sodium *tert*-pentoxide. A white precipitate was observed in the yellow liquid. The mixture was stirred for 15 min and a solution of 139 mg (0.667 mmol) of **17**

(29) Conia, J.-M.; Lamasset, J.-C. *Bull Soc. Chim. Fr.* **1967**, 1936.

in 1.5 mL of dry benzene was added rapidly. The addition was slightly exothermic and the yellow color dissipated. The mixture was stirred for 1 h and was filtered through a pad of silica gel. The adsorbent was rinsed with 1:9 ether–hexane. The solvent was evaporated and the crude product was purified by flash chromatography (1:4 ether–hexane) to afford 124 mg (90%) of **14** as a colorless liquid that was homogeneous by TLC: IR 3070, 1705, 1640, 1465, 1445, 1425, 1380, 1365, 1315, 1240, 1145, 1050, 1000, 950, 905 cm^{-1}; ^1H NMR δ 0.99 (3 H, s), 1.05 (3 H, s), 1.00–2.60 (13 H, m), 4.92 (2 H, dd), 5.74 (1 H, 2 dd); ^{13}C NMR δ 20.8, 22.7, 23.5, 27.3, 34.9, 35.0, 35.9, 37.4, 37.7, 38.7, 52.0, 11.8, 143.9, 215.6; MS, *m/e* 206 (M^+) 163, 125 (base), 107; TLC R_f 0.60 (1:3 ethyl acetate–hexane); HRMS, *m/e* 206.1669 (calcd for $C_{14}H_{22}O$ 206.1671).

2,3,4,5,6,7,8,9-Octahydro-7β-cyclopropyl-9β,10β-dimethyl-1(10*H*)-naphthalenone (15). In an adaptation of procedures by Conia[22] and Repic,[23] a solution of 19.5 mg (0.0945 mmol) of **14** in 200 μL of dry ether was added to 104 mg (1.60 mmol) of a Zn–Ag couple prepared from zinc granules and silver acetate. The mixture was treated with 60 μL (0.80 mmol) of diiodomethane and brought to reflux in a heated, ultrasonic bath. Sonication and reflux were continued for 2.5 h. Midway through the reaction time, 50 μL of dry ether was added to replenish the solvent. The mixture was cooled in an ice–water bath and diluted with 1 mL of ether. The dropwise addition of 0.5 mL of pyridine resulted in the formation of a thick, white precipitate. The precipitate was removed by filtration, and the filtrate was passed through a column of silica gel and evaporated to give 22.3 mg of yellow liquid. Flash chromatography (1:19 ether–hexane) yielded 14.1 mg (68%) of **15** as a colorless liquid that was homogeneous by TLC: IR 3090, 1710, 1475, 1450, 1435, 1385, 1375, 1325, 1250, 1155, 1065, 1020, 9960, 845, 825 cm^{-1}; ^1H NMR δ (–)0.03–(+)0.03 (1 H, m), 0.06–0.12 (1 H, m), 0.12–0.25 (2 H, m), 0.29–0.38 (1 H, m), 0.99 (3 H, s), 1.04 (3 H, s), 1.05–2.30 (13 H, m); ^{13}C NMR δ 3.0, 3.1, 17.6, 20.8, 2.8, 23.6, 28.0, 35.0, 35.3, 36.8, 37.8, 38.9, 39.0, 52.1, 215.9; MS, *m/e* 220 (M^+), 177, 150, 149, 134, 125 (base), 121, 107, 96; HRMS, *m/e* 220.1834 (calcd for $C_{15}H_{24}O$ 220.1828).

2,3,4,5,6,7,8,9-Octahydro-7β-isopropyl-9β,10β-dimethyl-1-(10*H*)-naphthalenone (13). According to the method of Oppolzer,[16] 18.2 mg of **15** in 1 mL of freshly distilled acetic acid was hydrogenated in a Parr apparatus at 3–4 atm for 18 h in the presence of 50 mg of PtO_2 catalyst. The reaction mixture was filtered through glass wool and the reaction vessel was rinsed with 3 mL of ether. The solvents were evaporated to give 24.0 mg of colorless liquid. Flash chromatography (1:9 ether–hexane) yielded 16.6 mg (90%) of **13** as a colorless liquid: IR 1710, 1470, 1450, 1385, 1370, 1150 cm^{-1}; ^1H NMR δ 0.85 (3 H, d, J = 6.6 Hz), 0.89 (3 H, d, J = 6.6 Hz), 0.97 (3 H, s), 1.05 (3 H, s), 1.00–2.60 (14 H, m); ^{13}C NMR δ 19.4, 20.1, 20.7, 22.8, 23.8, 24.6, 32.9, 33.9, 35.0, 35.5, 37.8, 38.8, 39.5, 52.4, 216.0; HRMS, *m/e* 222.1982 (calcd for $C_{15}H_{26}O$ 222.1985).

2,3,4,5,6,7,8,9-Octahydro-7-methylene-9β,10β-dimethyl-1-(10*H*)-naphthalenone (20). To 1.67 g of potassium *tert*-butoxide in 24 mL of dry *tert*-butyl alcohol under N_2 was added a solution of 1.92 g of **2** in 12 mL of dry THF. A precipitate began to form as the addition neared completion. The mixture was stirred for 10 h at room temperature and then poured into 100 mL of saturated aqueous NH_4Cl. The organic layer was removed and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layers were washed with 30 mL of brine, dried over Na_2SO_4, and evaporated to give 0.830 g of a white precipitate suspended in a yellow oil. Flash chromatography (hexane, 1:9 ether–hexane, 1:4 ether–hexane, ether) gave 0.275 g (21%) of **6** and 0.468 g (68%) of **20** as a pale yellow liquid that was homogenous by TLC: IR 3080, 1710, 1655, 1465, 1390, 1325, 1055, 890 cm^{-1}; ^1H NMR δ 0.87 (3 H, s), 0.97 (3 H, s), 1.35–1.47 (3 H, m), 1.75 (1 H, d, J = 13.4 Hz), 1.80–2.55 (7 H, m), 2.76 (1 H, d, J = 13.4 Hz), 4.63 (1 H, s), 4.70 (1 H, s); ^{13}C NMR δ 18.3, 21.3, 23.8, 30.4, 32.8, 36.7, 37.0, 38.8, 41.0, 53.9 109.6, 144.6, 215.2; MS, *m/e* 192 (M^+), 177 ($M^+ - CH_3$), 159, 149 (base), 134, 121, 107, 93, 79; TLC, R_f 0.53 (1:3 ethyl acetate–hexane); HRMS, *m/e* 192.1526 (calcd for $C_{13}H_{20}O$ 192.1515).

1,2,3,4,5,6,7,8-Octahydro-7-(hydroxymethyl)-9β,10β-dimethyl-1(10*H*)-naphthalenols (21). In an adaptation of procedures of Brown,[27] a solution of 438 mg (2.28 mmol) of **20** in 2.5 mL of dry THF under N_2 was cooled to –15 °C and treated with 4.6 mL (2.3 mmol, 0.5 M in THF) of 9-borabicyclo[3.3.1]nonane (9-BBN) over 5 min. The yellow solution was stirred for 0.5 h at –15 °C and for 0.5 h at 0 °C. The mixture was cooled again to –15 °C and 13.2 mL (6.61 mmol, 0.5 M in THF) of 9-BBN was added over 15 min. The mixture was allowed to warm to room temperature over 0.5 h and stirred for 2 h. The mixture was then cooled in an ice–water bath and treated with 5 mL of aqueous 3 M NaOH, followed by dropwise addition of 5 mL of aqueous 30% H_2O_2. The mixture was brought to room temperature and stirred for 0.5 h. The aqueous layer was saturated with K_2CO_3 and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 2.26 g of colorless oil. Flash chromatography (1:1 ethyl acetate–hexane) afforded diols with TLC R_f's 0.40 (92.1 mg, 19%), 0.34 (157 mg, 32%), and 0.26 and 0.22 (combined 174 mg, 36%) (ethyl acetate). Spectral data for the diol with R_f 0.34 included the following: ^1H NMR δ 0.75–2.05 (15 H, m), 1.06 (6 H, s), 3.30–3.60 (3 H, m); HRMS, *m/e* 194.1661 (calcd for $C_{13}H_{24}O_2 - H_2O$ 194.1671).

A sample of the diol with R_f 0.40 was oxidized with PCC in CH_2Cl_2, as in the preparation of **17** and **16**, to afford **17**: IR 2720, 1735, 1710, 1475, 1455, 1440, 1390, 1380, 1325, 1255, 1160, 1060, 1035, cm^{-1}; ^1H NMR δ 0.96 (s), 1.10 (s), 1.00–2.65 (m), 9.63 (s). Likewise, the diol with R_f 0.22 was converted to **17**: IR 2730, 1730, 1710, 1475, 1455, 1440, 1395, 1380, 1330, 1265, 1160, 1060, 1035, cm^{-1}; ^1H NMR δ 0.98 (s), 1.11 (s), 1.00–2.65 (m), 9.63 (s).

2,3,4,5,6,7,8,9-Octahydro-7α-formyl-9β,10β-dimethyl-1-(10*H*)-naphthalenone (22). To a solution of 305 mg (1.41 mmol) of PCC[18] in 2.2 mL of dry CH_2Cl_2 was added 100 mg (0.471 mmol) of diol **21** with R_f 0.34. After 1 h, the brown mixture was diluted with 3 mL of ether and decanted. The tar was triturated with ether (5 × 5 mL), causing the residue to become granular. The combined ether extracts were filtered through silica gel and evaporated to give 89.1 mg (91%) of **22** as a colorless liquid that was homogeneous by TLC: IR 2730, 1735, 1710, 1470, 1395, 1160, 1060, 930 cm^{-1}; ^1H NMR δ 0.88 (3 H, s), 1.08 (3 H, s), 1.00–2.60 (13 H, m), 9.67 (1 H, s); ^{13}C NMR δ 20.2, 21.4, 23.9, 32.5, 33.9 36.9, 38.8, 45.5, 51.7, 203.5, 216.0; TLC R_f 0.60 (ethyl acetate); HRMS, *m/e* 208.1462 (calcd for $C_{13}H_{20}O_2$ 208.1464).

2,3,4,5,6,7,8,9-Octahydro-7α-vinyl-9β,10β-dimethyl-1-(10*H*)-naphthalenone (23). As in the preparation of **14**, 174 mg (0.486 mmol) of methyltriphenylphosphonium bromide was suspended in 1 mL of dry benzene under N_2 and treated with 51 mg (0.47 mmol) of sodium *tert*-pentoxide. The mixture was stirred at room temperature for 15 min and then cooled to 0 °C in an ice–water bath. A solution of 81.0 mg (0.389 mmol) of **22** in 1 mL of dry benzene was added via syringe. The mixture was brought to room temperature and stirred for 30 min. The mixture was filtered through silica gel and the solvent was evaporated to give 174 mg of oil. Flash chromatography (1:4 ether–hexane) afforded 76.1 mg (95%) of **23** as a colorless liquid that was homogeneous by TLC: IR 3090, 1710, 1645, 1465, 1390, 1050, 945, 915 cm^{-1}, ^1H NMR δ 0.80 (3 H, s), 1.07 (3 H, s), 1.10–2.70 (13 H, m), 4.85–5.05 (2 H, dd), 5.65–5.80 (1 H, m); ^{13}C NMR δ 16.7, 21.8, 24.9, 27.2, 32.0, 35.7, 36.3, 37.0, 38.5, 39.4, 52.9, 112.6, 143.3, 216.5; MS, *m/e* 206 (M^+), 191 ($M^+ - CH_3$), 163, 125 (base), 105, 98; TLC R_f 0.52 (1:3 ethyl acetate–hexane); HRMS, *m/e* 206.1665 (calcd for $C_{14}H_{22}O$ 206.1671).

2,3,4,5,6,7,8,9-Octahydro-7α-cyclopropyl-9β,10β-dimethyl-1(10*H*)-naphthalenone (25). As in the preparation of **15**, a solution of 21.4 mg (0.104 mmol) of **23** in 200 μL of dry ether and 0.06 mL (0.08 mmol) of diiodomethane was added to 104 mg (1.60 mmol) of a Zn–Ag couple prepared from zinc granules and silver acetate. The mixture was heated at reflux and irradiated in an ultrasonic bath for 2 h. The mixture was cooled to 0 °C and then diluted with 1 mL of ether. The dropwise addition of 0.5 mL of pyridine resulted in the formation of a thick precipitate. The white solid was removed by filtration, and the orange filtrate was passed through a column of silica gel. Evaporation of the solvent gave 23.3 mg of yellow liquid. Flash chromatography (1:4 ether–hexane) afforded 14.4 mg (63%) of **25** as a colorless liquid that was homogenous by TLC: IR 3090, 1710, 1470, 1440, 1325, 1160, 1050, 1025, 945 cm^{-1}; ^1H NMR δ (–)0.08–(+)0.10 (2 H, m), 0.27–0.57 (3 H, m), 0.78 (3 H, s), 0.98 (3 H, s), 0.60–2.77 (13 H, m); ^{13}C NMR δ 3.2, 3.4, 16.7, 17.6, 21.9 24.9, 27.8, 32.0, 36.1, 37.0, 38.1, 38.9, 40.4, 53.1, 216.9; TLC R_f 0.44 (1:4 ether–hexane); HRMS, *m/e* 220.1839 (calcd for $C_{15}H_{24}O$ 220.1828).

(±)-Valeranone (1). As in the preparation of **13**, a solution of 11.8 mg (0.0535 mmol) of **25** in 1 mL of freshly distilled acetic acid was hydrogenated in a Parr apparatus at 3–3.5 atm for 19 h in the presence of 30 mg of PtO_2 catalyst. The reaction mixture was filtered and evaporation of the solvent gave 18.5 mg of colorless liquid. Flash chromatography (1:9 ether–hexane) gave 12.5 mg of a 9:1 mixture of diastereomeric alcohols **26**. Data for the separated major isomer included the following: IR 3480, 1735 (acetic acid, trace), 1465, 1380, 1370, 1255, 1200, 1180, 1055, 1030, 975, 960; ^{1}H NMR δ 0.83 (6 H, d), 1.01 (3 H, s), 1.02 (3 H, s), 0.80–1.90 (14 H, m), 3.30 (1 H, s), 4.05 (1 H, t); TLC R_f 0.26 (1:4 ether–hexane). To a solution of 30 mg (0.14 mmol) of PCC in 100 μL of dry CH_2Cl_2 was added a solution of 8.2 mg (0.036 mmol) of the major isomer that was separated from the mixture **26** in 200 μL of dry CH_2Cl_2. The reaction mixture was stirred for 1 h, decanted, triturated with ether (4 × 1 mL), and filtered through silica gel to give 8.1 mg of crude **1**. Flash chromatography (1:19 ether–hexane) afforded 7.0 mg (86%) of **1** as a colorless liquid that was homogeneous by TLC: IR 1710, 1460, 1435, 1390, 1380, 1325, 1275, 1250, 1160, 1050, 940, 835 (IR of natural (−)-**1**:[6] 1695, 1451, 1420, 1374, 1362, 1305, 1258, 1238, 1148, 1040, 934, 827 cm^{-1}); ^{1}H NMR δ 0.81 (3 H, s), 0.86 (6 H, d), 1.06 (3 H, s), 1.15–2.45 (13 H, m) [^{1}H NMR of authentic (−)-**1**:[6] δ 0.81 (s), 0.86 (d), 1.06 (s), 1.15–2.45 (m)]; ^{13}C NMR δ 16.8, 19.8, 20.0, 21.8, 24.7, 24.9, 32.1, 32.9, 36.2, 37.0, 37.5, 38.5, 38.6, 53.1, 217.2; TLC R_f 0.45 (1:4 ether–hexane).

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Registry No. (±)-**1**, 50302-14-2; (±)-*cis*-**2**, 113998-31-5; (±)-*trans*-**2**, 113998-50-8; (±)-**6**, 113998-33-7; **7**, 113998-51-9; **7** (chloride), 113998-32-6; **8**, 1122-20-9; **9**, 37457-15-1; **10**, 113998-34-8; **11**, 113998-35-9; (±)-*cis*-**12**, 113998-36-0; (±)-*trans*-**12**, 113998-49-5; (±)-**13**, 50302-15-3; (±)-**14**, 113998-37-1; (±)-**15**, 113998-38-2; (±)-**16**, 113998-39-3; (±)-**17**, 113998-40-6; (±)-**20**, 113998-41-7; (±)-4β,7β-**21**, 113998-42-8; (±)-4α,7β-**21**, 113998-46-2; (±)-4β,7α-**21**, 113998-47-3; (±)-4α,7α-**21**, 113998-48-4; (±)-**22**, 113998-43-9; (±)-**23**, 113998-44-0; (±)-**25**, 113998-45-1; (±)-4α-**26**, 114127-47-8; (±)-4β-**26**, 114127-46-7; $Br(CH_2)_2Br$, 106-93-4.

Synthesis, Characterization, and Thermolysis of 7-Amino-7-azabenzonorbornadienes

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Synthetic routes are given for the facile preparation of mono- and dibenzo-7-amino-7-azanorbornadienes **4** and **5**. For **5** the key intermediate *N*-benzylisoindole (**9**) was treated with benzyne, generated via reaction of *o*-bromofluorobenzene with magnesium in THF to give tertiary amine **10**. *N*-Bromosuccinimide-mediated debenzylation of **10** gave secondary amine **13**, which was then aminated by *O*-(mesitylsulfonyl)hydroxylamine (MSH). Similarly amination of monobenzo amine **25** gave **4**, which, however, proved to be unstable and therefore best isolated as the [(9-fluorenylmethyl)oxy]carbonyl (FMOC) derivative **27**. Deblocking of **27** by means of diethylamine gave amine **4** as needed. Upon standing overnight in ether, free **4** underwent self-reduction to give dihydro derivative **29**, whereas, in the presence of ethyl phenylpropiolate, cinnamate and dihydrocinnamate esters were formed. The simplest explanation for these results is that a reducing species is ejected upon thermolysis of **4**. Nonstereospecific reduction occurred in contrast to the stereospecific reduction that occurred in the presence of authentic diimide precursor **23**. Compounds **4** and **5** upon thermolysis in the presence of both acetic acid and propiolate ester led to stereospecific cis reduction. These results suggest that under acidic conditions protonated diimide is generated from both **4** and **5** whereas under neutral conditions **4** may yield azamine or a mixture of azamine and diimide. Direct involvement of **4** and **20** in reduction processes was, however, not eliminated. Thermolysis of **5** under neutral conditions is dependent on the solvent used. In DMF, clean conversion to 9,10-dihydroanthracene occurs whereas complex reaction mixtures are observed in benzene, chloroform, or THF.

Introduction

Although unstable under ordinary conditions, diimide **1** has been generated by a variety of techniques[1] and is now a well-characterized species, most important as a transiently produced reducing agent. The situation is otherwise in the case of the isomeric azamine **2** (aminonitrene, 1,1-diazene).[1-3] On the other hand, there is a long history of studies related to the 1,1-disubstituted derivatives[4] of **2**, and recently some of these species have even been obtained as stable entities in solution.[5]

1 **2**

Some time ago,[6] we initiated a study of the possible thermal elimination of the azamine fragment **2** from a series of 7-amino-7-azanorbornadienes **3–5**. In the

(1) For brief reviews of theoretical questions and early experimental efforts on diimide and azamine, see: (a) Pasto, D. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 2290. (b) Casewit, C. J.; Goddard, W. A., III *J. Am. Chem. Soc.* **1980**, *102*, 4057.

(2) In this paper we use the nomenclature adopted by Smith in his definitive work: Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N–N Bonds*; Benjamin/Cummings: Reading, MA, 1983; p 212.

(3) For a recent study of the possible matrix isolation of azamine and references to earlier work, see: Sylwester, A. P.; Dervan, P. B. *J. Am. Chem. Soc.* **1984**, *106*, 4648.

(4) For reviews on the chemistry of substituted azamines, see: (a) Lemal, D. M. In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; p 345. (b) Ioffe, B. V.; Kuznetsov, M. A. *Russ. Chem. Rev. (Engl. Transl.)* **1972**, *41*, 131. (c) Anselme, J.-P. *Nippon Kagaku Zasshi* **1971**, *92*, 1065. (d) Hünig, S. *Helv. Chim. Acta* **1971**, *54*, 1721.

(5) (a) Hinsberg, W. D., III; Schultz, P. G.; Dervan, P. B. *J. Am. Chem. Soc.* **1982**, *104*, 766. (b) McIntyre, D. K.; Dervan, P. B. *J. Am. Chem. Soc.* **1982**, *104*, 6466. (c) Miller, R. D.; Gölitz, P.; Janssen, J.; Lemmens, J. *J. Am. Chem. Soc.* **1984**, *106*, 1508.

(6) Barr, D. Ph.D. Thesis, University of Massachusetts, Amherst, MA, 1965.

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