bath for the first hour. The solvent was then removed on the rotary evaporator and the residue taken up in H_2O and neutralized with saturated sodium bicarbonate solution. This was extracted with 2 × 50 mL portions of methylene chloride. The combined organic phase was dried over anhydrous sodium sulfate and the solvent removed on the rotary evaporator to give a sticky yellow solid. Trituration of this with 1:4 hexane/ether and recrystallization of the resulting solid from 2-propanol provided 1.04 g (50%) of pure **16**; mp 203–209 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.76 (3 H, s, CH_3^b), 2.28 (3 H, s, CH_3^a), 2.99 (1 H, d, J = 1 Hz, H_b), 3.72 (3 H, s, CO_2CH_3), 3.73 (3 H, s, CO_2CH_3), 3.88 (1 H, br s, H_a), 4.71 (1 H, s, H_c), 7.33 (4 H, m, aromatic); mass spectrum, m/e 345 (M^+). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.98; H, 5.65; N, 4.19.

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Registry No. **1**, 34824-58-3; **2**, 59259-01-7; **3**, 96557-29-8; **4**, 1074-16-4; **5**, 96557-30-1; **6**, 96557-31-2; **6** (Br derivative), 96557-36-7; **7**, 96557-32-3; **8**, 96575-47-2; **9**, 96575-48-3; **10a**, 96557-33-4; **10b**, 96614-26-5; **11**, 96557-34-5; **13**, 96575-49-4; **16**, 96557-35-6; $MeC(NH_2)$=$CHCO_2Me$, 14205-39-1; $AcCH_2CO_2Me$, 105-45-3; $CH_2(OH)CH_2(OH)$, 107-21-1; H_2S, 7783-06-4.

Supplementary Material Available: Crystallographic data, including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **10b** (6 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Bridging with Olefins

George D. Hartman,* Wasyl Halczenko,* and Brian T. Phillips

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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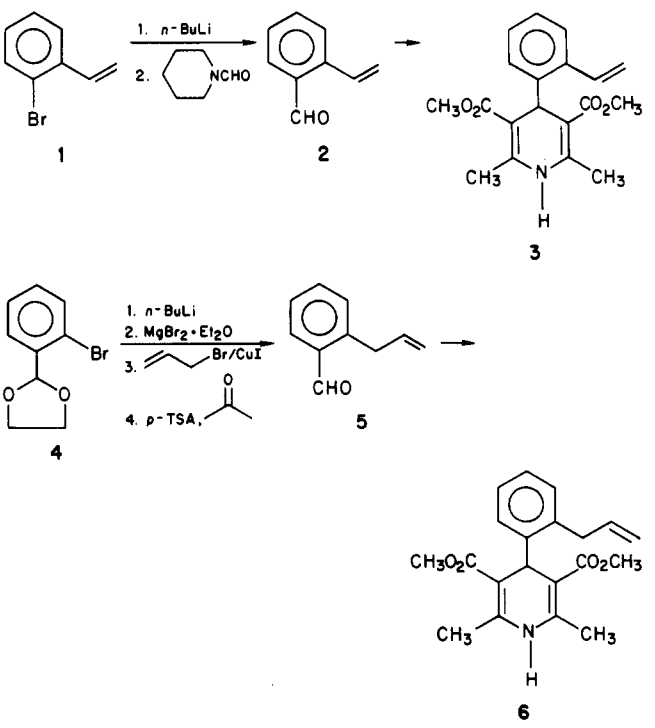
Acid-catalyzed cyclization of 4-(2-alkenylphenyl)-1,4-dihydropyridines affords products derived from formal [4 + 2] cycloaddition processes between the olefinic moiety and a vinyl iminium species. Mechanistically, these products arise by sequential intramolecular capture of cationic intermediates. These molecules constitute novel, conformationally rigid analogues of biologically important 1,4-dihydropyridines.

As described in the accompanying paper, 4-aryl-1,4-dihydropyridines have gained importance as therapeutic agents in cardiovascular disease. Our particular interest has been in the preparation of novel, conformationally constrained dihydropyridine analogues with which to study the dihydropyridine receptor. Herein we report the preparation of the carbocyclic analogues of the compounds described in this earlier paper, via a novel intramolecular iminium ion mediated bis-cyclization process.

The intramolecular capture of iminium ions by various nucleophiles has proven to be a highly effective method in the total synthesis of complex alkaloids.[1] The observation[2] that a vinyl iminium species could be generated from 4-aryl-1,4-dihydropyridines prompted us to explore the capture of this reactive intermediate with simple carbon–carbon double bonds. From a consideration of molecular models we anticipated that intramolecular capture of the dihydropyridine/iminium species would be optimum in molecules **3** and **6**, where the electrophilic iminium carbon is positioned respectively seven or eight atoms from the olefin terminus. Pseudoaxial orientation of the 4-aryl substituent allows for extremely favorable stereoelectronic orientation of the terminal olefin relative to the iminium carbon at C-2.

The preparation (Scheme I) of dimethyl 2,6-dimethyl-4-(2-ethenylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3**) involved metalation of commercially available 2-bromostyrene followed by formylation[3] with *N*-formylpiperidine to give **2**. Treatment of **2** under Hantzsch conditions with methyl 3-aminocrotonate and methyl acetoacetate provided **3** in 26% yield. The generation of dimethyl 2,6-dimethyl-4-[2-(3-propenyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**6**) required metalation of acetal **4** with *n*-butyllithium and cation exchange with magnesium bromide etherate to give the corresponding Grignard reagent. Coupling of this with allyl bromide and deprotection of the aldehyde under standard conditions provided 2-(3-propenyl)benzaldehyde (**5**). Formation of **6** under Hantzsch conditions via treatment with methyl

Scheme I



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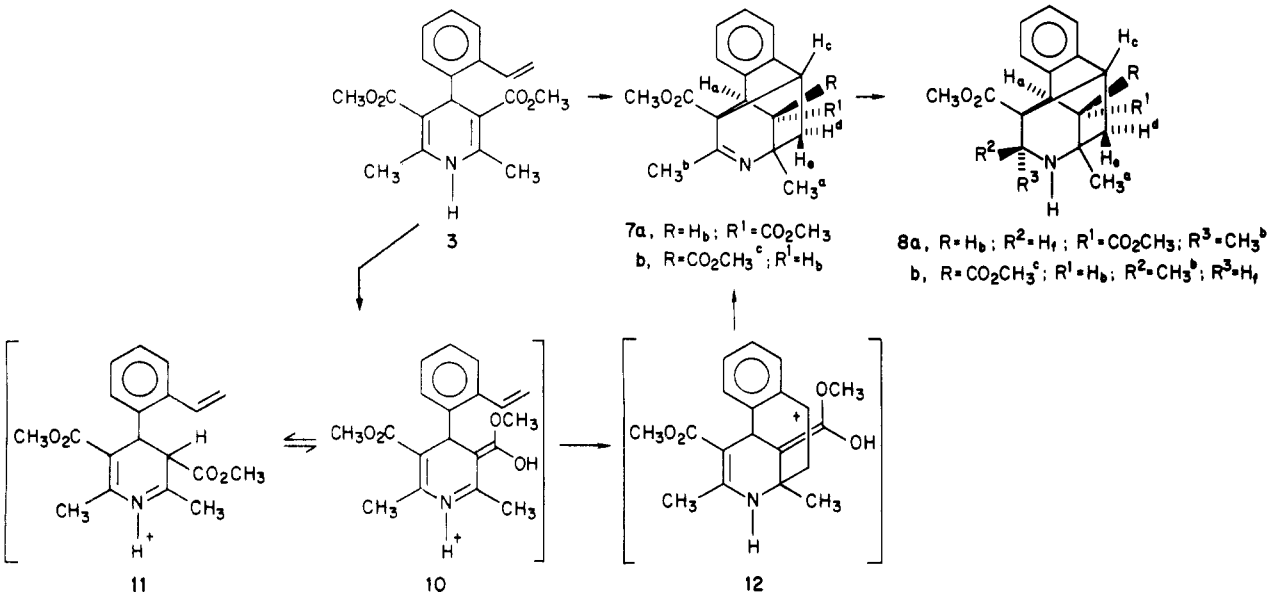
0022-3263/85/1950-2427$01.50/0

Scheme II



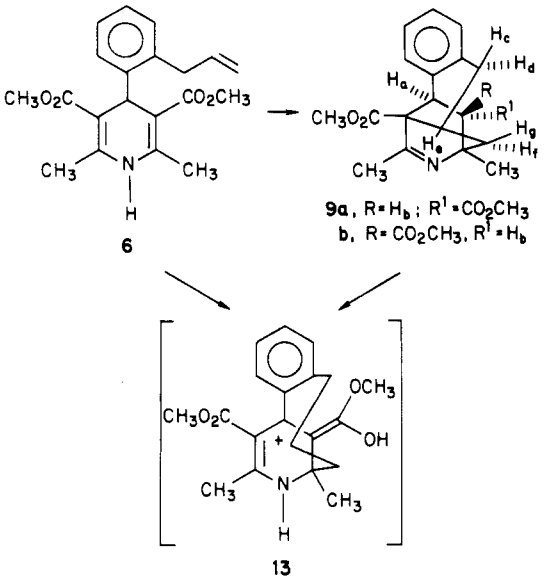
3-aminocrotonate and methyl acetoacetate proceeded smoothly.

We have found that treatment of dimethyl 2,6-dimethyl-4-(2-ethenylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3**) with gaseous hydrogen chloride in chloroform at room temperature for 6 h afforded in 80% yield a mixture of dimethyl 4,4a,9,9a-tetrahydro-1,3-dimethyl-3,9-methano-3*H*-indeno[2,1-*c*]pyridine-9a,10α-dicarboxylate (**7a**) (Scheme II) and its diastereoisomer **7b** in a ratio of ca. 3:2. These products were also produced, albeit in lower yield and in varying ratios, when **3** was treated with titanium tetrachloride or trimethylsilyl trifluoromethanesulfonate in chloroform. Only small amounts of **7a** and **7b** were formed when **3** was heated at 120 °C in xylene for 24 h in base-washed glassware. The structure identification of **7a** and **7b** derives from ^{1}H NMR spectra comparison with compound **9a**, for which X-ray data are available (vide infra), as well as from elemental analysis and mass spectral data. Characteristically, the 360-MHz ^{1}H NMR spectra of **7a** and **7b** show four different methyl group absorptions, and distinction between **7a** and **7b** is made on the basis of the coupling constant between H_a and H_b, which for **7a** is 2.4 Hz and for **7b** is 9.0 Hz. Interestingly, the α-isomer displays ester group methyl resonances that are of similar chemical shift (δ 3.67 and 3.70), whereas the corresponding resonances of the β-isomer are more widely separated (δ 3.42 and 3.65). The explanation for this effect, which provides a rapid spectroscopic method for distinguishing diastereoisomers in this series, is that the methyl ester at the diastereomeric center of the β-isomer is shifted to higher field by the anisotropic effect of the adjacent phenyl ring.

Reduction of **7a** with $NaBH_4$ in methanol at room temperature gave predominately **8a**, in which hydride was delivered from the β-face of the molecule since the α-face is shielded by the ester function. The structure of **8a** was proven by NOE experiments illustrating the syn relationship of H_a to CH_3^b and of H_f to H_c. In contrast, similar reduction of **7b** provided, as the predominant product, **8b**, in which hydride has attacked from the α-face of the molecule. The structure of **8b** was proven by NOE experiments illustrating the syn relationship of H_c and CH_3^b.

In similar fashion, treatment of dimethyl 2,6-dimethyl-4-[2-(3-propenyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**6**) (Scheme III) with excess titanium tetrachloride in chloroform afforded in 74% yield dimethyl 3,4,4a,5,10,10a-hexahydro-1,3-dimethyl-3,10-methanobenzo[*g*]isoquinoline-10a,11α-dicarboxylate (**9a**) and its diastereoisomeric β-isomer **9b** in a ratio of ca. 12:1. These same products also were generated by treatment of **6** with hydrogen chloride gas or trimethylsilyl trifluoromethanesulfonate in chloroform, however heating **6** in xylene resulted only in aromatization to the pyridine. The structure of **9a** was proved by single-crystal X-ray determination,[4] and an ORTEP representation is shown in Figure 1. It is interesting to note the constrained, pseudoaxial orientation of the phenyl ring.

Scheme III



The mechanism of formation (Scheme II) of these cycloadducts most likely involves initial protonation or Lewis acid complexation of **3** on either oxygen or carbon to yield the iminium ions **10** and **11**, respectively. Then, as shown for **10**, intramolecular attack by the carbon–carbon double bond on the electrophilic iminium species would provide cation **12**, which is suitably positioned for final ring closure

(4) Private communication from Dr. James P. Springer and Jordan Hirshfield, Merck Sharp & Dohme Research Laboratories, Rahway, NJ.

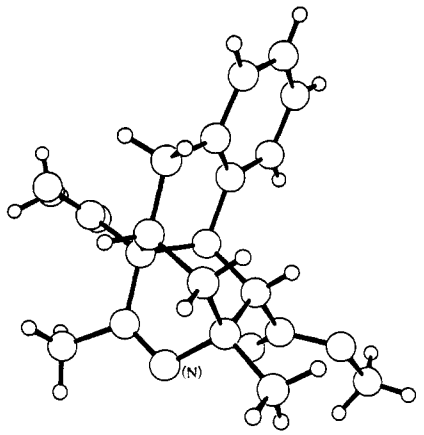


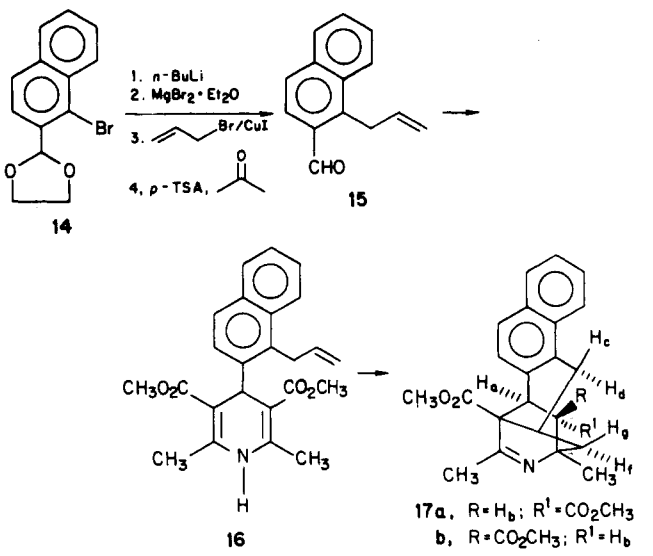
Figure 1. ORTEP representation of compound **9a**.

via covalent interaction with the nucleophilic aminocrotonate. The facility with which this reaction proceeds with the unactivated carbon–carbon double bonds[5] of **3** and **6** attests to the highly reactive nature of the iminium species, as well as to the favorable geometric relationships provided. One might argue that the formation of benzyl cation **12** is an important driving force; however, cyclization of **6**, which recruits the secondary cation **13**, proceeds at roughly the same rate. Further, the present method is complementary to that presented in the accompanying paper, in that here the dihydropyridine initiates cyclization by acting as an electrophile, whereas in the preparation of the heteroatom-bridged analogues, it performed initially as a nucleophile.

Although capture of iminium species by internal nucleophiles such as activated phenyl rings[6] and heterocycles[1,7] has typically concluded with proton elimination from the intermediate cation to regenerate the aromatic nucleus, the nucleophilic attack of aminocrotonate in cation **12** to conclude bis cyclization is not without precedent. Wenkert et al.[8] have demonstrated elegant methodology for the construction of the *Aspidosperma* alkaloid skeleton employing an iminium ion initiated cyclization followed by internal trapping of the cationic intermediate by an enol. Taken together, these cases highlight the opportunities for construction of complex polycyclic systems via trapping with nucleophiles that are chemically silent to the iminium ion generating conditions.

Conceptually, there is also the possibility that this transformation involves an acid-catalyzed concerted[9] [4 + 2] cycloaddition process. There is ample precedent detailing the ability of 1- and 2-azadienes to participate in both normal[10–14] and inverse[15,16] electron demand [4 + 2] cycloaddition processes. A somewhat closer analogy to the present work is that of cation polar cycloaddition,[17] wherein reaction is between electron-deficient quaternary "dienes" such as isoquinolinium[18] or acridizinium[19] salts and electron-rich olefins such as vinyl ethers. However, the mechanism of these transformations is still under study.[20,21]

Scheme IV



We have, in an effort to probe the scope of this methodology, studied the cyclization of dimethyl 2,6-dimethyl-4-[1-(2-propenyl)naphth-2-yl]-1,4-dihydropyridine-3,5-dicarboxylate (**16**). Compound **16** was prepared from **14** (Scheme IV) in direct analogy with the synthesis of **6** from **4**. Treatment of **16** with titanium tetrachloride in chloroform provided a 69% yield of cycloadduct **17a**, accompanied by a trace of diastereomer **17b**. Cyclization of **16** was also effected with gaseous hydrogen chloride to provide varying yields and diastereomeric ratios of **17a** and **17b**. No cyclization products were obtained when **16** was refluxed in xylene for 3 days in base-washed glassware.

In summary, we have demonstrated a novel iminium ion mediated bis-cyclization method for the synthesis of rigid, carbon-bridged analogues of 4-aryl-1,4-dihydropyridines. We are continuing to study the capture of the hydropyridine/iminium species with other nucleophiles.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60, an EM-390, or a Nicolet NT-360 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a LKB-9000S mass spectrometer at 70 eV. *N*-Formylpiperidine, methyl acetoacetate, methyl 3-aminocrotonate, and 2-bromostyrene were obtained from Aldrich and all were used without purification.

2-Ethenylbenzaldehyde (2). To a solution of 21.0 g (0.115 mol) of 2-bromostyrene (1) dissolved in tetrahydrofuran and cooled to −78 °C under nitrogen was added 0.115 mol of *n*-butyllithium

(5) For analogous reactivity in electron-transfer-initiated photocyclization reactions of iminium salts, see: Tiner-Harding, T.; Ullrich, J. W.; Chiu, F.-T.; Chen, S.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 3360.
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(hexane) dropwise while keeping the internal temperature <–65 °C. After the mixture was stirred for 1 h at –65 °C, 14.15 g (0.125 mol) of *N*-formylpiperidine in 10 mL of tetrahydrofuran was added dropwise, and the resulting solution was stirred overnight with gradual warming to room temperature.

The reaction mixture was then quenched with 50 mL of saturated ammonium chloride solution and diluted with 500 mL of ether. The organic phase was separated, washed with two 50-mL portions of 3 N hydrochloric acid, 50 mL of saturated sodium bicarbonate, and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give **2** as a pale yellow oil: 14.0 g (92%); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.44 (1 H, dd, =CH_2), 5.64 (1 H, dd, =CH_2), 7.1–8.0 (5 H, m, aromatic + =CH), 10.25 (1 H, s, CHO).

Dimethyl 2,6-Dimethyl-4-(2-ethenylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3). To 14.0 g (0.106 g) of **2** in 100 mL of methanol were added 12.20 g (0.106 mol) of methyl 3-aminocrotonate and 12.31 g (0.106 mol) of methyl acetoacetate, and the resulting solution was heated at reflux under nitrogen for 3 days. The solvent was then remooed in vacuo and crystallization induced by trituration with 50 mL hexane. The resulting yellow solid was collected and subsequently purified by flash chromatography on silica gel (230–400 mesh), eluting with 1:2 hexane/ether to provide pure **3**: 8.2 g (24%); mp 140–148 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.30 (6 H, s), 3.57 (6 H, s, CO_2CH_3), 5.31 (1 H, s), 5.31 (1 H, dd, =CH_2), 5.48 (1 H, dd, =CH_2), 5.86 (1 H, br, s, NH), 7.0–7.8 (5 H, m, aromatic + =CH).

Dimethyl 4,4a,9,9a-Tetrahydro-1,3-dimethyl-3,9-methano-3*H*-indeno[2,1-*c*]pyridine-9a,10α-dicarboxylate (7a) and 10β-Isomer (7b). A solution of 4.0 g (0.122 mol) of **3** in 50 mL of chloroform was cooled in ice, and gaseous HCl was bubbled through for 0.5 h. After the reaction mixture was stirred at room temperature for an additional hour, it was diluted with 50 mL of chloroform and neutralized with ammonium hydroxide. The organic layer was separated and the aqueous phase extracted with two 50-mL portions of chloroform. The combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo to give a yellow oil. Trituration with hexane/petroleum ether gave 2.8 g (70%) of a tan solid, which was a mixture of **7a** and **7b**. This was purified by flash chromatography on silica gel (230–400 mesh), eluting with 1:4 hexane/ether to give 0.86 g (22%) of **7b**, R_f 0.4, followed by 1.25 g (31%) of **7a**, R_f 0.3.

7a: mp 160–161 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.45–1.55 (2 H, m, H_d and H_e), 1.47 (3 H, s, CH_3[a]), 2.21 (3 H, s, CH_3[b]), 2.50 (1 H, d, H_B, J = 2 Hz), 3.38 (1 H, d of t, H_c), 3.67 (3 H, s, CO_2CH_3), 3.70 (3 H, s, CO_2CH_3), 3.80 (1 H, br s, H_a, J = 2 Hz), 7.10 (4 H, m, aromatic). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.92; H, 6.51; N, 4.41.

7b: mp 104–105 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.40 (1 H, m, H_e), 1.43 (3 H, s, CH_3[a]), 2.12 (1 H, d, H_d), 2.15 (3 H, s, CH_3[b]), 2.36 (1 H, d of d, H_b, J = 11, 2 Hz), 3.42 (3 H, s, CO_2CH_3[c]), 3.43 (1 H, d, H_c), 3.65 (3 H, s, CO_2CH_3), 3.72 (1 H, d, H_a, J = 11 Hz), 7.10 (4 H, m, aromatic). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.67; H, 6.46; N, 4.47.

Dimethyl 2,3,4,4a,9,9a-Hexahydro-1,3α-dimethyl-3,9-methano-1*H*-indeno[2,1-*c*]pyridine-9a,10α-dicarboxylate (8a). To 0.5 g (1.5 mmol) of **7a** in 8 mL of methanol at room temperature under nitrogen was added 0.076 g (2.0 mmol) of sodium borohydride, and the resulting suspension was stirred overnight.

The solvent was removed in vacuo, the residue was taken up in 25 mL of H_2O, and this was extracted with four 50-mL portions of methylene chloride. The combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo to give an oil. This was purified by flash chromatography on E. Merck silica gel (230–400 mesh), eluting with 3% methanol/methylene chloride to give 0.27 g (52%) of **8a** as a white solid: R_f 0.3; mp 104–106 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.96 (3 H, s, CH_3[a]), 1.26 (3 H, d, CH_3[d]), 1.48 (1 H, d, H_d, J = 12 Hz), 1.89 (1 H, br s, NH), 2.23 (1 H, dd, H_e), 2.38 (1 H, d, H_b, J = 2 Hz), 3.50 (1 H, d, H_c), 3.51 (3 H, s, CO_2CH_3), 3.66 (1 H, q, H_f), 3.74 (4 H, s, H_a and CO_2CH_3), 7.05–7.27 (4 H, m, aromatic). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.27; H, 7.14; N, 3.99.

Dimethyl 2,3,4,4a,9,9a-Hexahydro-1,3β-dimethyl-3,9-methano-1*H*-indeno[2,1-*c*]pyridine-9a,10β-dicarboxylate (8b), Maleate Derivative. To 0.52 g (1.6 mmol) of **7b** in 15 mL of methanol at room temperature under nitrogen was added 0.076 g (2.0 mmol) of sodium borohydride, and this was stirred overnight. The solvent was then removed in vacuo, and the residue was diluted with 20 mL of H_2O and extracted with four 50-mL portions of ether. The combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo to leave an oil. This was purified by flash chromatography on silica gel (230–400 mesh), eluting with 3% methanol/methylene chloride to afford 0.5 g (95%) of pure **8b** as an oil. This was dissolved in 5 mL of acetone, and a solution of 0.176 g (1.5 mmol) of maleic acid in 10 mL of acetone was added and this diluted with 30 mL of ether. After the mixture was stirred at room temperature for 1 h, the maleate salt had crystallized out and was collected by filtration: mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.25 (3 H, s, CH_3[a]), 1.33 (3 H, d, CH_3[b]), 1.88 (1 H, d, H_d, J = 15 Hz), 2.20 (1 H, dd, H_e, J = 15, 11 Hz), 3.38 (1 H, d, H_b, J = 11 Hz), 3.41 (3 H, s, CO_2CH_3[c]), 3.51 (3 H, s, CO_2CH_3), 3.74 (1 H, d, H_c, J = 11 Hz), 3.82 (1 H, d, H_a, J = 11 Hz), 3.95 (1 H, q, H_f), 6.05 (2 H, s, CH=CH of maleic acid), 7.0–7.28 (4 H, m, aromatic). Anal. Calcd for $C_{19}H_{23}NO_4 \cdot C_4H_4O_4$: C, 62.01; H, 3.15; N, 6.11. Found: C, 61.82; H, 3.01; N, 6.14.

2-(3-Propenyl)benzaldehyde (5). To a solution of 0.5 g (2.5 mmol) of 2-bromobenzaldehyde ethylene glycol acetal (**4**) in 10 mL of ether cooled to –78 °C under nitrogen was added 2.5 mmol of *n*-butyllithium (hexane) dropwise and the resulting yellow solution stirred at –78 °C for 0.5 h. Then, at –78 °C, 0.65 g (2.5 mmol) of magnesium bromide etherate was added portionwise, and after stirring for 15 min, the suspension was allowed to warm to 0 °C over 15 min. Then 0.047 g (2.5 mmol) of cuprous iodide was added at 0 °C, and after the resulting mixture was stirred for 5 min, a solution of 0.30 g (2.5 mmol) of allyl bromide in 5 mL of ether was added. The reaction mixture was allowed to warm to room temperature overnight.

The reaction mixture was cooled in ice, quenched with 20 mL of dilute hydrochloric acid, and extracted with two 40-mL portions of ether. The combined organic extracts were washed with saturated sodium bicarbonate solution and brine and dried. The solvent was removed in vacuo to give an oil, which was taken up in acetone, and a catalytic amount of *p*-toluenesulfonic acid was added. After 16 h at room temperature the solvent was removed in vacuo, and the residue was taken up in chloroform, washed with two 15-mL portions of saturated sodium bicarbonate and brine, and stripped to yield 0.3 g (82%) of crude **5** as a yellow oil, which was used directly in the next step. **5** had R_f 0.7 on silica gel, eluting with 1% ethyl acetate/chloroform: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.80 (2 H, m), 5.0 (2 H, m), 5.95 (1 H, m), 7.0–7.8 (4 H, m).

Dimethyl 2,6-Dimethyl-4-[2-(3-propenyl)]phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (6). To 0.37 g (2.5 mmol) of **5** in 12 mL of methanol were added 0.29 g (2.5 mmol) of methyl 3-aminocrotonate, 0.30 g (2.5 mmol) of methyl acetoacetate, and 1 drop of concentrated ammonium hyroxide, and the resulting solution was refluxed under nitrogen for 5 days. The solvent was removed in vacuo to leave a yellow oil, which was purified by flash chromatography on silica gel (230–400 mesh), eluting with 1% ethyl acetate/chloroform to give 0.36 g (42%) of **6** as a white solid: mp 133–134 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.33 (6 H, s, CH_3), 3.61 (6 H, s, CO_2CH_3), 3.76 (2 H, d, CH_2), 5.15 (1 H, m, =CH_2), 5.22 (1 H, s, CH), 5.62 (1 H, br s, NH), 7.20–7.35 (4 H, m, aromatic). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.30; H, 6.66; N, 4.19.

Dimethyl 3,4,4a,5,10,10a-Hexahydro-1,3-dimethyl-3,10-methanobenzo[*g*]isoquinoline-10a,11α-dicarboxylate (9a) and 11β-Isomer (9b). To a solution of 0.051 g (0.15 mmol) of **6** in 2.5 mL of chloroform was added 0.057 g (0.3 mmol) of titanium tetrachloride at room temperature under nitrogen. After the reaction mixture was stirred for 2 h, it was neutralized with saturated sodium bicarbonate solution and the organic phase separated. The aqueous phase was extracted with two 5-mL portions of chloroform, the combined organic phases were dried, and the solvent was removed in vacuo to give an oil. This was purified by flash chromatography on silica gel (230–400 mesh), eluting with 2% methanol/chloroform to give 3.0 mg (7%) of **9b** (R_f 0.26) and 38 mg (74%) of **9a** (R_f 0.18). In contrast, inverse addition of **6** to a 4 molar excess of titanium chloride resulted in the formation of **9b** as the predominant product.

9a: mp 150–152 °C; IR (KBr pellet) 3450, 2950, 1720, 1620, 1480, 1430, 1360, 1260, 1180, 850, 760, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.24 (1 H, dd, H_f, J = 14, 6 Hz), 1.46 (3 H, s), 1.80 (1 H, dd, H_g, J = 15, 12 Hz), 2.16 (3 H, s), 2.38 (1 H, d, H_b, J = 3 Hz), 2.49 (1 H, m, H_e), 2.68 (1 H, d, H_d, J = 18 Hz), 3.09 (1 H, dd, H_c, J = 18, 6 Hz), 3.68 (3 H, s), 3.73 (3 H, s), 3.78 (1 H, dd, H_a, J = 6, 3 Hz), 7.1 (4 H, m); high-resolution mass spectrum, calcd 341.1627, found 341.1624. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.37; H, 6.80; N, 4.19.

9b: mp 96–107 °C; IR (KBr pellet) 3450, 2950, 1730, 1630, 1430, 1270, 1250, 1170, 710, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.38 (3 H, s), 1.63 (1 H, m, H_g), 2.11 (3 H, s), 2.26 (1 H, dd, H_f, J = 13, 5 Hz), 2.51 (1 H, m, H_e), 2.58 (1 H, dd, H_b, J = 12, 3 Hz), 2.78 (1 H, d, H_d, J = 18 Hz), 3.06 (1 H, dd, H_c, J = 18, 6 Hz), 3.26 (3 H, s), 3.66 (3 H, s), 3.68 (1 H, dd, H_a, J = 12, 3 Hz), 7.1 (4 H, m, aromatic); high-resolution mass spectrum, calcd 341.1627, found, 341.1628. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.03; H, 6.96; N, 4.12.

1-(3-Propenyl)-2-naphthaldehyde (15). To a solution of 4.19 g (15.0 mmol) of 1-bromo-2-naphthaldehyde ethylene glycol acetal in 60 mL of ether cooled to −78 °C in a dry ice/acetone bath was added dropwise 15.0 mmol of *n*-butyllithium/hexane. The solution was stirred 30 min, and 3.87 g (15.0 mmol) of magnesium bromide etherate was added through Gooch tubing. The resulting suspension was stirred 15 min and then warmed to 0 °C. Then 0.29 g (1.5 mmol) of cuprous iodide was added, the mixture was stirred 5 min, and a solution of 1.81 g (15 mmol) of allyl bromide in 15 mL of ether was added dropwise. The mixture was stirred overnight while gradually warming to room temperature. The reaction was quenched by addition of 3 N HCl (50 mL), and the mixture was stirred 15 min. The layers were separated, and the aqueous layer was extracted with two 100-mL portions of ether. The combined organic extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 3.10 g of oil. The oil was flash chromatographed on a column of E. Merck silica gel (230–400 mesh) eluted with 4% EtOAc/hexane to give 2.37 g (81%) of **15** as an oil: ^1H NMR ($CDCl_3$, 60 MHz) δ 4.3 (2 H, m), 5.0 (2 H, m), 6.1 (1 H, m), 7.8 (6 H, m), 10.4 (1 H, s).

Dimethyl 2,6-Dimethyl-4-[1-(3-propenyl)-2-naphthyl]-1,4-dihydropyridine-3,5-dicarboxylate (16). A solution of 2.16 g (11.0 mmol) of 1-(3-propenyl)-2-naphthaldehyde (**15**), 1.28 g (11.0 mmol) of methyl acetoacetate, 1.27 g (11.0 mmol) of methyl 3-aminocrotonate, and concentrated NH_4OH (5 drops) in 11 mL of methanol was refluxed for 72 h. The solution was cooled to room temperature and the precipitate filtered off to give 2.01 g (46%) of **16**. An analytical sample, mp 180–183 °C, was obtained by recrystallization from ethanol: IR (KBr pellet) 3420, 2950, 1700, 1680, 1480, 1430, 1210, 1110, 1090, 910, 800, 770, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.3 (6 H, s), 3.6 (6 H, s), 4.2 (2 H, d, J = 6 Hz), 5.1 (2 H, m), 5.6 (1 H, s), 5.8 (1 H, br s), 6.0 (1 H, m), 7.6 (5 H, m), 8.1 (1 H, m). Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.63; H, 6.44; N, 3.58. Found: C, 73.38; H, 6.50; N, 3.28.

Dimethyl 7,7a,10,11,11a,12-Hexahydro-8,10-dimethyl-7,10-methanonaphth[1,2-*g*]isoquinoline-7a,13α-dicarboxylate (17a) and 13β-Isomer (17b). To a solution of 0.59 g (1.5 mmol) of **16** in 22 mL of chloroform was added 0.57 g (3.0 mmol) of titanium tetrachloride at room temperature under nitrogen. The resulting dark orange solution was stirred overnight. The reaction was quenched with H_2O and neutralized with saturated sodium bicarbonate solution, and the layers were separated. The aqueous phase was extracted with two 50-mL portions of chloroform, the combined organic extracts were washed with brine and dried, and the solvent was removed in vacuo. The resulting gummy solid was purified by flash chromatography on E. Merck silica gel (230–400 mesh), eluting with 2% methanol/chloroform to give 0.59 g of **17a** as a glassy solid with R_f 0.33. This was triturated with hexane to give 0.41 g (69%) of **17a** was a white solid. Inverse addition of **16** to a 5 molar excess of titanium chloride alternatively provided **17b** (R_f 0.28) as the major product in 40% yield.

17a: mp 193–195 °C; IR (KBr pellet) 3450, 2940, 2330, 1730, 1620, 1430, 1260, 1190, 1170, 810, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.25 (1 H, dd, H_f, J = 14, 6 Hz), 1.47 (3 H, s), 1.87 (1 H, dd, H_g, J = 14, 13 Hz), 2.20 (3 H, s), 2.47 (1 H, d, H_b, J = 3 Hz), 2.70 (1 H, m, H_e), 3.13 (1 H, d, H_d, J = 18 Hz), 3.32 (1 H, dd, H_c, J = 18, 6 Hz), 3.64 (3 H, s), 3.76 (3 H, s), 3.93 (1 H, br s, H_a), 7.16 (1 H, d, J = 8 Hz), 7.5 (2 H, m), 7.67 (1 H, d, J = 8 Hz), 7.81 (1 H, d, J = 8 Hz), 7.91 (1 H, d, J = 8 Hz); high-resolution mass spectrum, calcd 391.1783, found 391.1779. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.63; H, 6.44; N, 3.58. Found: C, 73.34; H, 6.56; N, 3.44.

17b: mp 192–198 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 1.40 (3 H, s), 1.71 (1 H, m, H_g), 2.14 (3 H, s), 2.28 (1 H, dd, H_f, J = 13, 5 Hz), 2.67 (1 H, dd, H_b, J = 12, 2 Hz), 2.71 (1 H, m, H_e), 3.21 (1 H, d, H_d), 3.25 (3 H, s), 3.32 (1 H, dd, H_c, J = 18, 6 Hz), 3.60 (3 H, s), 3.83 (1 H, dd, H_a, J = 12, 3 Hz), 7.07 (1 H, d, J = 8 Hz), 7.48 (2 H, m), 7.58 (1 H, d, J = 8 Hz), 7.78 (1 H, d, J = 8 Hz), 7.92 (1 H, d, J = 8 Hz); high-resolution mass spectrum, calcd 391.1783, found 391.1783. Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.63; H, 6.44; N, 3.58. Found: C, 73.25; H, 6.62; N, 3.74.

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Supplementary Material Available: Crystallographic data including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **9a** (6 pages). Ordering information is given on any current masthead page.

Acetoacetylation with 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one: A Convenient Alternative to Diketene

Robert J. Clemens* and John A. Hyatt

Research Laboratories, Eastman Chemicals Division, Eastman Kodak Company, Kingsport, Tennessee 37662

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The diketene/acetone adduct, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, efficiently acetoacetylates aliphatic and aromatic alcohols, amines, and thiols. These acetoacetylation reactions are fast and stoichiometric, require no catalysis, and give only volatile byproducts.

The acetoacetylation of nucleophiles is a prosaic but extremely important reaction as acetoacetates are widely used synthetic intermediates in both laboratory and industrial preparations. Most of these acetoacetylations are effected with diketene,[1] a highly reactive, lachrymatory, and toxic reagent. Unfortunately, few alternatives are available.[2]

(1) For acetoacetylation procedures using diketene, see: Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722 and ref 14 therein.

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