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[3 + 2] Cycloaddition Reactions of 4-Alkyl-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium Inner Salts

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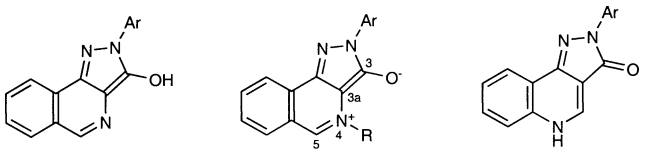
Received February 5, 2003

Abstract: Heating dipolarophiles with 4-alkyl-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium hydroxide inner salts results in [3 + 2] cycloaddition across positions 3a and 5 of the aromatic system to give the [3 + 2] cycloadducts in good yield. When the 4-alkyl substituent is a 2-acetate ester and the methylene group can be deprotonated, a second mode of [3 + 2] cycloaddition becomes available for the resulting anion (across the side chain methine group and position 5 of the aromatic system) and occurs under basic conditions, allowing either of two modes of [3 + 2] cycloaddition to be selected by appropriate choice of reaction conditions.

Benzodiazepine receptor ligands have been of long standing interest in medicinal chemistry due to the wide range of pharmacological actions they mediate.[1] Cook and co-workers[2] reported the investigation of 2-aryl-2*H*-pyrazolo[4,3-*c*]isoquinolinium-3-ols **1** and corresponding inner salts **2** (R = Bn), bearing a benzyl group at the 4-position, as potential ligands at benzodiazepine receptors (Figure 1).[3] The compounds showed low affinity at the benzodiazepine receptors, consistent with a pharmacophore model for binding to the benzodiazepine receptor proposed by the authors. Related 2-arylpyrazolo[4,3-*c*]-quinolin-3-ones **3**, however, show nanomolar binding to benzodiazepine receptors, with a range of activity from full agonists to antagonists,[4] while other derivatives of the same class show potent antitumor activity associated with inhibition of mammalian topoisomerase II.[5] As part of a pharmaceutical discovery program we became concerned with the investigation of the properties of compounds related to **1** and **2**.



1 **2** **3**

FIGURE 1. Compounds **1**−**3**.

The inner salt **5** was prepared by the route[6] shown in Scheme 1 (PMB = 4-methoxybenzyl), analogous to the procedure described by Cook and co-workers for related compounds.[7] The condensation of keto-ester **4** with 4-trifluoromethylphenylhydrazine proceeded with concomitant oxidation of the isoquinoline ring to produce the fully aromatic, intensely purple, formally zwitterionic compound **5** directly. Compound **5** then underwent loss of the PMB group upon heating in trifluoroacetic acid to give the acidic (pK_a ∼6) phenolic compound **6**. The alkoxide anion resulting from deprotonation of the hydroxy compound **6** could, as a result of delocalization of the negative charge, in principle undergo electrophilic attack at any of three positions: N-1, N-4, or the alkoxide oxygen. We observed, however, that upon treatment with potassium carbonate and appropriate alkyl halides in DMF, alkylation occurred predominantly at N-4 to give compounds **7** and **8** as the only isolated products, although the formation of minor amounts of byproducts resulting from alkylation at the alternative alkylation positions is a possibility.

The valence bond structure by which the inner salts **2** are represented suggested that these compounds might undergo [3 + 2] cycloaddition reactions of the type observed with azomethine ylides[8] across positions 3a and 5, as shown in Scheme 2, to give compounds containing the novel 6,7-benzo-3,4,11-triazatricyclo[6.2.1.$0^{1,5}$]undeca-4,6,9-triene (or -4,6-diene) heterocyclic ring system. The azomethine ylide motif here is part of an extended aromatic system, and the ready oxidation that occurs during the formation of **5** suggests a significant degree of aromatic stabilization of the inner salt structure. Furthermore, the [3 + 2] cycloaddition requires the disruption of two aromatic rings. We therefore decided to investigate the possibility of a [3 + 2] cycloaddition in

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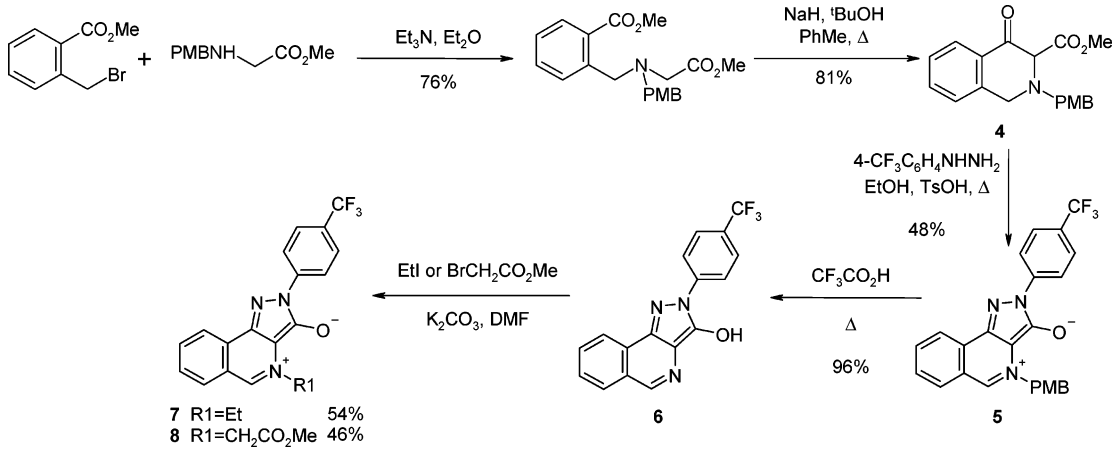
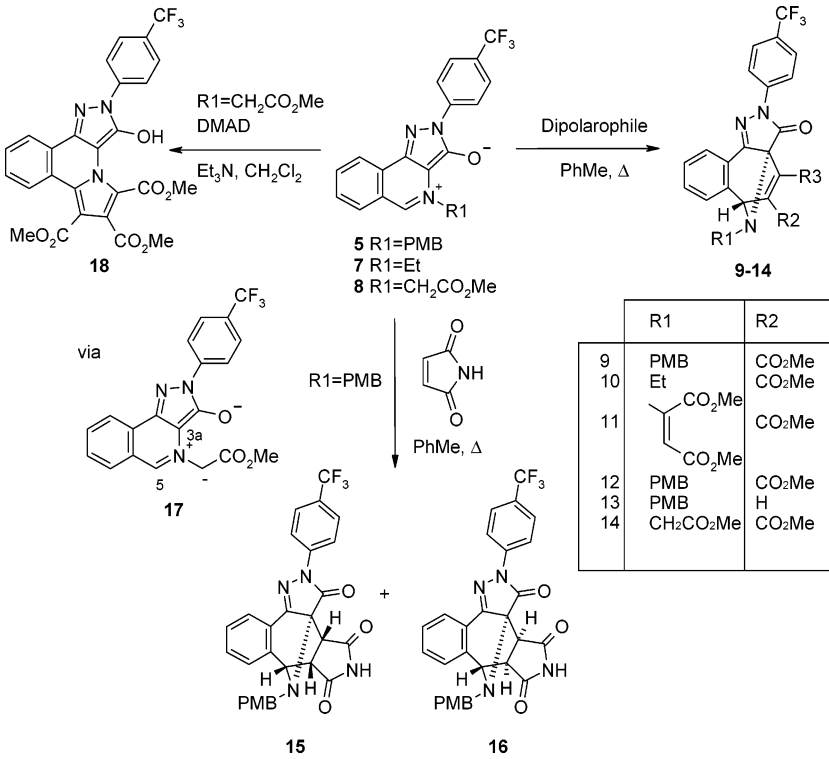
10.1021/jo034160f CCC: $25.00
Published on Web 09/27/2003

SCHEME 1. Synthesis of 4-Alkyl-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium Inner Salts



SCHEME 2. 1,3-Cycloaddition Reactions of 4-Alkyl-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium Inner Salts



	R1	R2	R3
9	PMB	CO_2Me	CO_2Me
10	Et	CO_2Me	CO_2Me
11		CO_2Me	CO_2Me
12	PMB	CO_2Me	H
13	PMB	H	CO_2Me
14	CH_2CO_2Me	CO_2Me	CO_2Me

this type of aromatic system. To test the feasibility of a dipolar cycloaddition, we first heated a solution of compound **5** in toluene with dimethyl acetylenedicarboxylate (DMAD) as a dipolarophile. After 1 h, the deep purple color of the solution had disappeared, and the cycloadduct **9** was isolated in 89% yield. Compound **7** underwent a similar reaction to give the cycloadduct **10** in 86% yield. The reaction of compound **6** with DMAD was also investigated. Upon treatment with a 4-fold excess of DMAD in toluene a cycloaddition addition product **11** (52% yield) was indeed produced. The *E*-stereochemistry of the side chain C═C bond was assigned on the basis of the observation of NOEs between the singlets in the ^{1}H NMR spectrum assigned to the bridgehead and olefinic CH groups. Potentially, formation of **11** could occur through alkylation of N-4 by conjugate addition to the DMAD to form the 1,3-dipole species for this cycloaddition, although dipole formation via tautomerization in which the C-3 hydroxyl proton is transferred to N-4 (i.e., to give a structure **2** with R = H), cycloaddition, and a subsequent conjugate addition is also possible.

The reactions of **5** with maleimide and with methyl propiolate were investigated to probe the stereo- and regiochemistry of the cycloaddition reaction. Treatment of **5** with excess maleimide in toluene gave, after chromatography, a 2:1 mixture of compounds, tentatively assigned as a mixture of **15** and **16**, respectively the *exo* and *endo* cycloaddition products, from which the major isomer **15** could be isolated by recrystallization (ethyl acetate/isohexane). When a solution of **15** in DMSO-d_6 was heated at 100 °C for 24 h, the solution became purple, and ^{1}H NMR examination showed that the cycloadduct had largely decomposed to reform the inner salt **5**. Equilibration of the isomers **15** and **16** had also occurred (the ratio of **5**:**15**:**16** was approximately 8:2:1).

The cycloaddition is therefore reversible, and the observed *exo*/*endo* ratio for the reaction of **5** with maleimide probably represents the thermodynamic ratio. Treatment of **5** with excess methyl propiolate in toluene gave a mixture of regioisomers, which were separable by chromatography: **12** (32% yield) and **13** (59% yield). These regioisomers could be distinguished by the observation in the ^{1}H NMR spectrum of **13** of coupling between the bridgehead and olefinic H atoms, whereas the corresponding signals are singlets in the ^{1}H NMR spectrum of **12**.

Finally, we investigated the cycloaddition reactions of compound **8**. The methylene group of the C-4 substituent in **8** was anticipated to be sufficiently acidic to enable facile deprotonation. Two modes of [3 + 2] cycloaddition could be envisaged for the resulting anion **17**: first, across positions 3a and 5 of the aromatic system or second, across the side chain methine group and position 5. The second mode was expected to be preferred, since only one aromatic ring is disrupted by the cycloaddition. Treatment of compound **8** with DMAD in the presence of triethylamine (4 equiv) at room temperature, for 20 h, afforded compound **18** in 44% yield. Formation of **18** can be rationalized as the product of the expected mode [3 + 2] cycloaddition of DMAD across the side chain methine group of anion **17** and C-5, followed by oxidative aromatization of the resulting cycloadduct. In contrast, if the side chain deprotonation is suppressed, addition should occur as above, resulting in cycloaddition across positions 3a and 5. Indeed, treatment of compound **8** with DMAD in the presence of acetic acid, added to suppress possible deprotonation of the side chain by the tertiary amine of the product, gave compound **14** in 86% yield.

Thus, 4-alkyl-3-hydroxy-2*H*-pyrazolo[4,3-*c*]isoquinolinium inner salts were found to undergo cycloaddition with dipolarophiles to give cycloadducts containing the novel 6,7-benzo-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene (or -4,6-diene) heterocyclic ring system. In the cycloaddition of compound **8**, with DMAD, alternative modes of [3 + 2] cycloaddition could be selected by appropriate choice of reaction conditions.

Experimental Section

Methyl 1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)methyl-4-oxo-3-isoquinolinecarboxylate (4). Methyl 2-bromomethylbenzoate[9] (23.47 g, 102 mmol) and triethylamine (15.7 mL, 11.4 g, 112 mmol) were dissolved in dry diethyl ether (200 mL) under a nitrogen atmosphere. Methyl *N*-[(4-methoxyphenyI)-methyl]glycinate[10] (23.6 g, 112 mmol) was added dropwise. The mixture was heated under reflux for 16 h and allowed to cool to room temperature. Water was added, and the organic phase was separated. The aqueous phase was then extracted three times with ethyl acetate. The combined organic extract was washed with brine and dried (Na_2SO_4). Filtration and evaporation of the solution followed by further purification of the residues by column chromatography, eluting with ethyl acetate/isohexane (1:9), gave methyl 2-{*N*-(methoxycarbonylmethyl)-*N*-[(4-methoxyphenyl)methyl]aminomethyl}benzoate as an oil (27.85 g, 77.9 mmol, 76%). The oil was dissolved in dry toluene (150 mL) and added dropwise to a refluxing suspension of oil-free sodium hydride (from 4.37 g of 60% sodium hydride) in dry toluene (300 mL) and 2-methylpropan-2-ol (2.0 mL). The heating was continued for 12 h. The mixture was allowed to cool to room temperature, then poured onto saturated ammonium chloride solution, and extracted three times with ethyl acetate. The combined organic extract was washed with brine and dried (Na_2SO_4). Filtration and evaporation followed by purification by column chromatography, eluting with diethyl ether/isohexane (1:4), gave the subtitle compound as an oil (20.41 g. 62.7 mmol, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) (major component, enol tautomer) δ 3.60 (2H, s), 3.81 (3H, s), 3.91 (5H, s), 6.86 (2H, d, J = 8.7 Hz), 7.09 (1H, d, J = 8.7 Hz), 7.25 (2H, d, J = 7.4 Hz), 7.35−7.43 (2H, m), 7.77 (1H, d, J = 8.8 Hz), 11.58 (1H, s).

3-Hydroxy-4-[(4-methoxyphenyl)methyl]-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinolinium Inner Salt (5). Compound **4** (30.14 g, 92.9 mmol), 4-(trifluoromethyl)-phenylhydrazine (20.55 g, 128.3 mmol), and 4-toluenesulfonic acid hydrate (0.56 g, 2.94 mmol) in ethanol was heated under reflux for 18 h, and then the solution was allowed to cool. The precipitated solid was collected by filtration, washed with ether, and then dried under vacuum to give compound **5** as a dark purple solid (15.49 g, 34.5 mmol, 37%), mp 220−221 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.72 (3H, s), 6.08 (2H, s), 6.95 (2H, m), 7.71 (2H, m), 7.79 (1H, td, J = 7.8 Hz, 1.2 Hz), 7.81 (2H, d, J = 9.0 Hz), 7.95 (1H, td, J = 7.7 Hz, 1.2 Hz), 8.15 (1H, d, J = 7.7 Hz), 8.35 (1H, d, J = 8.1 Hz), 8.6 (2H, d, J = 8.1 Hz), 8.96 (1H, s); MS (APCI) m/z 450 [(MH)$^+$]. Anal. Calcd for $C_{25}H_{18}F_3N_3O_2$: C, 66.81; H, 4.04; N, 9.35; Found: C, 66.69; H, 4.26; N, 9.31. The solution was evaporated, and the residue was triturated with ether. The resulting solid was collected by filtration, washed with ether, and dried under vacuum to give further recovery of compound **5** (4.43 g, 9.9 mmol, 11%).

3-Hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]isoquinoline (6). Compound **5** (5.20 g, 11.6 mmol) in trifluoroacetic acid (100 mL) was heated under reflux for 8 h. The solution was evaporated, and the residue was coevaporated twice with toluene and then with methanol. The residue was triturated with ether to give a red solid (3.64 g, 11.1 mmol, 96%), mp >250 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98 (4H, m), 8.33 (4H, m), 9.06 (1H, broad s), 11.96 (1H, broad s). MS (APCI) m/z 330 (MH$^+$). Anal. Calcd for $C_{17}H_{10}F_3N_3O$: C, 62.01; H, 3.06; N, 12.76; Found: C, 61.73; H, 3.29; N, 12.65.

3-Hydroxy-4-ethyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium Inner Salt (7). Compound **6** (950 mg, 2.89 mmol) and potassium carbonate (2.6 g, 18.8 mmol) were stirred in DMF (50 mL), and then iodoethane (1.0 mL, 1.95 g, 12.5 mmol) was added. After 1 h of stirring at 25 °C, the solution was diluted with ethyl acetate, washed with water and then brine, dried ($MgSO_4$), filtered, and evaporated. Flash chromatography with methanol (2.5−5%) in dichloromethane followed by recrystallization from ethyl acetate/isohexane gave compound **7** (561 mg, 1.57 mmol, 54%) as a purple solid, mp 192−198 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (3H, t, J = 7.1 Hz), 4.89 (2H, q, J = 7.1 Hz), 7.78 (3H, m), 7.96 (1H, t, J = 7.5 Hz), 8.10 (1H, d, J = 8.1 Hz), 8.35 (1H, d, J = 7.8 Hz), 8.60 (2H, d, J = 8.4 Hz), 8.76 (1H, s). MS (APCI) m/z 358 (MH$^+$). Anal. Calc. for $C_{19}H_{14}F_3N_3O$: C, 63.86; H, 3.95.N, 11.76; Found: C, 63.92; H, 3.90; N, 11.90.

3-Hydroxy-4-methoxycarbonylmethyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo-[4,3-*c*]isoquinolinium Inner Salt (8). Prepared by a method analogous to that described for compound **7** by alkylation of compound **6** with methyl bromoacetate. Purification by flash chromatography with methanol (3%) in dichloromethane gave compound **8** (46%) as a purple solid, mp 149−152 °C: ^{1}H NMR (DMSO-d_6) δ 3.79 (3H, s), 5.84 (2H, s), 7.82 (3H, m), 8.04 (1H, t, J = 7.2 Hz), 8.19 (1H, d, J = 8.1 Hz), 8.41 (1H, d, J = 7.8 Hz), 8.56 (2H, d, J = 8.4 Hz), 8.71 (1H, s); MS (APCI) m/z 402 (MH$^+$).

6,7-Benzo-11-[(4-methoxyphenyl)methyl]-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene-9,10-dicarboxylic Acid Dimethyl Ester (9). A solution containing compound **5** (236 mg, 0.53 mmol), 2,6-di-*tert*-butyl-4-methylphenol (1 crystal), and dimethyl acetylenedicarboxylate (0.2 mL, 0.23 g, 1.63 mmol) in toluene (5 mL) was heated under reflux under a nitrogen atmosphere for 1 h. The solution was evaporated, and the residue was purified by

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chromatography using ethyl acetate/isohexane as the eluant to give cycloadduct **9** (276 mg, 0.47 mmol, 89%) as a colorless solid, mp 205−208 °C: ^{1}H NMR (400 MHz, DMSO) δ 3.52 (1H, d, J = 12.8 Hz), 3.62 (3H, s), 3.67 (3H, s), 3.70 (1H, d, J = 12.8 Hz), 3.74 (3H, s), 4.98 (1H, s), 6.77 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz), 7.40 (1H, m), 7.57 (2H, m), 7.89 (2H, d, J = 8.8 Hz), 8.01 (1H, m), 8.05 (2H, d, J = 8.8 Hz). MS (APCI$^+$) m/z 592 (100%, MH$^+$). Anal. Calcd for $C_{31}H_{24}F_3N_3O_6$: C, 62.94; H, 4.09; N, 7.10. Found: C, 62.67; H, 4.18; N, 7.03.

6,7-Benzo-11-ethyl-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene-9,10-dicarboxylic Acid Dimethyl Ester (10). Prepared by a method similar to that described for compound **9** from the reaction of compound **7** with dimethyl acetylenedicarboxylate and obtained as a colorless solid in 86% yield, mp 158−160 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, t, J = 7.2 Hz), 2.64 (2H, m), 3.68 (3H, s), 3.82 (3H, s), 5.02 (1H, s), 7.33 (1H, m), 7.46 (2H, m), 7.70 (2H, d, J = 8.6 Hz), 8.00 (1H, m), 8.19 (2H, d, J = 8.6 Hz). MS (APCI$^+$) m/z 500 (100%, MH$^+$). Anal. Calcd for $C_{25}H_{20}F_3N_3O_5$: C, 60.12; H, 4.04; N, 8.41. Found: C, 59.75; H, 4.18; N, 8.34.

6,7-Benzo-11-[*E*-1,2-bis(methoxycarbonyl)ethenyl]-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]-undeca-4,6,9-triene-9,10-dicarboxylic Acid Dimethyl Ester (11). Prepared by a method similar to that described for compound **9** from the reaction of compound **6** with dimethyl acetylenedicarboxylate and obtained as a colorless solid in 52% yield, mp 229−231 °C: ^{1}H NMR (300 MHz, DMSO) δ 3.47 (3H, s), 3.56 (3H, s), 3.65 (3H, s), 3.80 (3H, s), 5.06 (1H, s), 6.14 (1H, s), 7.57−7.71 (3H, m), 7.94 (2H, d, J = 8.9 Hz), 8.03 (1H, m), 8.12 (2H, d, J = 8.9 Hz). MS (APCI$^+$) m/z 614 (100%, MH$^+$). Anal. Calcd for $C_{29}H_{22}F_3N_3O_9$: C, 56.78; H, 3.61; N, 6.85. Found: C, 56.51; H, 3.58; N, 7.12. The *E*-stereochemistry of the side chain C=C bond was assigned on the basis of the observation of NOEs between the singlets at 5.06 and 6.14.

[3 + 2] Cycloaddition of Compound 5 and Maleimide. A solution containing compound **5** (203 mg, 0.45 mmol), 2,6-di-*tert*-butyl-4-methylphenol (1 crystal), and maleimide (193 mg, 1.99 mmol) in toluene (5 mL) was heated under reflux under a nitrogen atmosphere for 2 h. The solution was evaporated, and the residue was purified by chromatography using ether/isohexane as the eluant to give a colorless solid that was tentatively assigned as a 2:1 mixture of the *exo* (1*R*,8*S*,9*R*,13*S*) and *endo* (1*R*,8*S*,9*S*,13*S*) isomers (compounds **15** and **16**) of 6,7-benzo-14-[(4-methoxyphenyl)methyl]-2,10,12-trioxo-3-(4-trifluoromethylphenyl)-3,4,11,14-tetrazatetracyclo[6.5.1.0.^{1,5}0^{9,13}]-tetradeca-4,6-diene (252 mg, approximately quantitative yield). The major product **15** crystallized from ethyl acetate/isohexane, mp 220 °C (dec): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19 (1H, d, J = 12.3 Hz), 3.30 (2H, AB quartet), 3.66 (1H, d, J = 12.3 Hz), 3.77 (3H, s), 4.52 (1H, s), 6.76 (2H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.53 (2H, m), 7.70 (2H, d, J = 8.6 Hz), 8.09 (1H, m), 8.17 (2H, d, J = 8.6 Hz), 8.23 (1H, m), 10.88 (1H, broad). MS (APCI$^-$) m/z 545 (M − H$^+$). Anal. Calcd for $C_{29}H_{21}F_3N_4O_4$: C, 63.74; H, 3.87; N, 10.25. Found: C, 63.86; H, 3.81; N, 10.32. The stereochemical assignment was based the coupling pattern observed for the ^{1}H NMR signal assigned to the bridgehead hydrogen, which in compound **15** appears as a singlet (dihedral angle to neighboring proton ~90° for the *exo* isomer based on examination of a molecular model), whereas in the spectrum of the mixture the signal tentatively assigned to the corresponding hydrogen of the minor component **16** was a doublet (J = 6.9 Hz) (dihedral angle to neighboring proton ~0° for the *endo* isomer).

6,7-Benzo-11-[(4-methoxyphenyl)methyl]-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene-9-carboxylic Acid Methyl Ester (12) and 6,7-Benzo-11-[(4-methoxyphenyl)methyl]-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene-9-carboxylic Acid Methyl Ester (13). Prepared by a method similar to that described for compound **9** from the reaction of compound **5** with methyl propiolate. The crude product was purified by chromatography using ether/isohexane to give two compounds: compound **12** obtained as a colorless solid in 32% yield, and compound **13** obtained as an oil in 59% yield. Compound **12**: mp 197 °C, ^{1}H NMR (400 MHz, DMSO) δ 3.47 (1H, d, J = 12.8 Hz), 3.64 (1H, d, J = 12.8 Hz), 3.66 (3H, s), 3.69 (3H, s), 4.73 (1H, s), 6.74 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.4 Hz), 7.31 (1H, s), 7.33 (1H, m), 7.53 (2H, m), 7.87 (2H, d, J = 8.8 Hz), 7.98 (1H, m), 8.05 (2H, d, J = 8.8 Hz). MS (APCI$^+$) m/z 534 (100%, MH$^+$). Anal. Calcd for $C_{29}H_{22}F_3N_3O_4$: C, 65.29; H, 4.16; N, 7.88. Found: C, 64.94; H, 4.23; N, 7.83. Compound **13**: ^{1}H NMR (400 MHz, DMSO) δ 3.50 (1H, d, J = 13.2 Hz), 3.60 (4H, m), 3.67 (3H, s), 4.78 (1H, d, J = 3.0 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.37 (1H, m), 7.54 (2H, m), 7.77 (1H, d, J = 3.0 Hz), 7.88 (2H, J = 8.8 Hz), 7.98 (1H, m), 8.07 (2H, J = 8.8 Hz); MS (APCI$^+$) m/z 534 (100%, MH$^+$).

6,7-Benzo-11-(methoxycarbonyl)methyl-2-oxo-3-(4-trifluoromethylphenyl)-3,4,11-triazatricyclo[6.2.1.0^{1,5}]undeca-4,6,9-triene-9,10-dicarboxylic acid dimethyl Ester (14). A solution containing compound **8** (151 mg, 0.38 mmol), 2,6-di-*tert*-butyl-4-methylphenol (1 crystal), dimethyl acetylenedicarboxylate (0.3 mL, 0.35 g, 2.45 mmol), and acetic acid (0.15 mL) in toluene (5 mL) was heated under reflux under a nitrogen atmosphere for 1 h. The solution was partitioned between aqueous sodium bicarbonate and dichloromethane, the organic layer was separated, dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by chromatography using ether/isohexane as the eluant to give cycloadduct **14** (176 mg, 0.32 mmol, 86%) as a colorless solid, mp 164−166 °C: ^{1}H NMR (300 MHz, DMSO) δ 3.57 (3H, s), 3.63 (5H, m), 3.77 (3H, s), 5.38 (1H, s), 7.48 (1H, m), 7.57 (2H, m), 7.92 (2H, d, J = 8.6 Hz), 8.00 (1H, m), 8.13 (2H, d, J = 8.6 Hz); MS (APCI$^+$) m/z 544 (100%, MH$^+$). Anal. Calcd for $C_{26}H_{20}F_3N_3O_7$: C, 57.46; H, 3.71; N, 7.73. Found: C, 57.10; H, 3.77; N, 7.64.

3-Hydroxy-2-(4-trifluoromethylphenyl)-2*H*-pyrazolo[4,3-*c*]pyrrolo[2,1-a]isoquinoline-4,5,6-tricarboxylic Acid Trimethyl Ester (18). A solution containing compound **8** (16 mg, 0.040 mmol), dimethyl acetylenedicarboxylate (5.7 mg, 0.040 mmol), and triethylamine (0.021 mL, 15 mg, 0.15 mmol) in dichloromethane (10 mL) was stirred at room temperature for 20 h. The solution was evaporated, and the residue was purified by chromatography using ethanol (3%) in dichloromethane as the eluant to give cycloadduct **18** (9.6 mg, 0.017 mmol, 44%) as a pale yellow solid, mp 246−248 °C (dec): ^{1}H NMR (300 MHz, DMSO) δ 3.81 (3H, s), 3.90 (3H, s), 3.95 (3H, s), 7.77 (2H, m), 7.93 (2H, d, J = 8.7 Hz), 8.18 (2H, d, J = 8.7 Hz), 8.21 (1H, m), 8.28 (1H, m); MS (APCI$^+$) m/z 542 (100%, MH$^+$). Anal. Calcd for $C_{26}H_{18}F_3N_3O_7$: C, 57.66; H, 3.11; N, 7.60. Found: C, 57.68; H, 3.35; N, 7.76.

Acknowledgment. We thank Drs. Roger Bonnert and Dave Donald for helpful discussions. We also thank Drs. Mike Bernstein, Mark Dixon, and Richard Lewis for NMR spectra.

Supporting Information Available: ^{1}H NMR spectra of all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034160F