Synthesis of a Functionalized Rigid Bicyclo[2.2.1]heptane: A Useful Hapten for Eliciting Catalytic Antibodies

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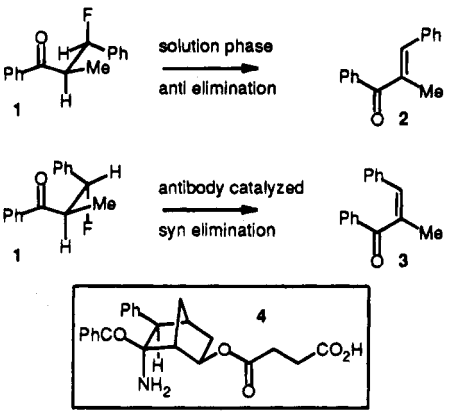
Of the unique capabilities provided by catalytic antibodies,[1] the potential catalysis of disfavored chemical reactions,[2] especially those not accessible under standard solution-phase conditions, offers rich opportunities. In recent studies, we disclosed the antibody catalysis of an acyclic syn elimination to provide a cis olefin (Scheme 1).[3] For acyclic systems, it is generally recognized that the anti elimination is greatly favored over syn elimination,[4] although the eclipsed syn coplanar versus staggered antiperiplanar transition state may be preferentially adopted in constrained cyclic systems.[5] The accounts of a rare acyclic syn elimination have been shown to provide a trans (*E*) olefin where the competing anti elimination suffers significant destabilizing steric interactions in route to the alternative cis olefin.[6] Notably, the syn elimination of an acyclic substrate to provide a cis (*Z*) olefin is the least favored and most formidable transformation of the group of elimination reactions and, to our knowledge, has not been selectively achieved.

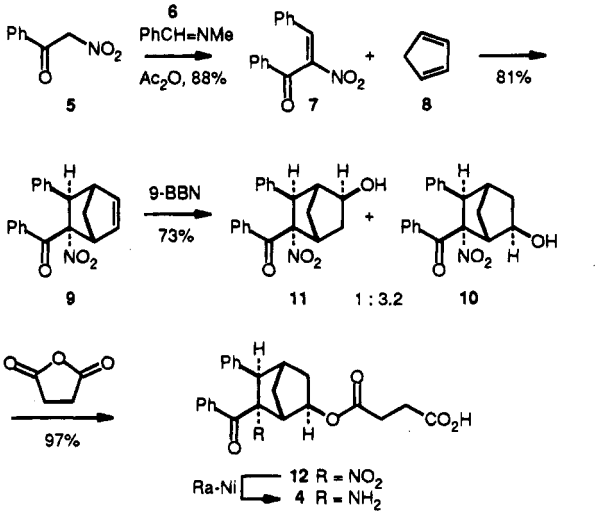
Herein, we provide details of the synthesis of **4**, the hapten utilized to elicit monoclonal antibodies capable of catalyzing the syn elimination of **1** to provide exclusively the cis olefin **3**. Key to the design of hapten **4** was the rigid eclipsed conformation embodied in the bicyclo[2.2.1]heptane ring system which dictated the presentation of the benzoyl and phenyl substituents in the desired eclipsed arrangement and the primary amine of **4** which was expected to induce an antibody functionality capable of acting as a base in the abstraction of the α-proton of **1**.

Condensation of α-nitroacetophenone (**5**) with *N*-methylbenzylideneimine (**6**) under the conditions detailed by Dornow and Menzel[7] (1.1 equiv of Ac_2O, Et_2O, reflux, 3 h, 88%) provided (*E*)-α-nitrochalcone (**7**) as the exclusive olefin isomer detected in the reaction mixture (Scheme 2). Treatment of **7** with freshly cracked cyclopentadiene (9.0 equiv of **8**, 45 °C, CH_2Cl_2, 24 h, 81%) provided a single predominant Diels–Alder adduct (**9**) derived from a [4 + 2] cycloaddition reaction through a transition state with the nitro substituent endo to the diene. Less than

Scheme 1



Scheme 2



1–3% of the diastereomeric exo adduct was detected. Notably, this Diels–Alder reaction proceeds near exclusively to provide the sterically less favored adduct **9**, presumably a consequence of a strong endo directing effect of the polarized nitro substituent.[8]

Clean exo hydroboration of **9** (1.25 equiv of 9-BBN, THF, 25 °C, 10 h; $NaOH–H_2O_2$, 73%) followed by oxidative workup provided a readily separable 3.2:1 mixture of **10** and **11**.[9] Acylation of **10** with succinic anhydride (2.0 equiv, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 4 h, 97%)[10] cleanly provided the hemisuccinate **12** as a highly crystalline intermediate. Single-crystal X-ray structure analysis[11] of **12** unambiguously established its structure confirming both the endo diastereoselectivity of the Diels–Alder reaction providing **9** and the regioselectivity of the exo hydroboration reaction to provide **10**. Finally, reduction of the nitro group of **12** to an amine (Raney Ni, H_2, $CH_3OH–H_2O$, 45 °C, 20 h) provided **4** along with variable amounts of the product resulting from complete reduction to the corresponding hydro-

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(11) The author has deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained upon request from the Director, Cambridge Crystallograhic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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carbon[12] with loss of the nitro group. Alternative reduction methods including the use of H_2–Pd/C (3 atm H_2, CH_3OH and CH_3OH–THF 9:1; 25 °C, 1–20 h), H_2–PtO_2 (3 atm H_2, CH_3OH–THF 9:1, 25 °C, 5 h), or transfer hydrogenation (HCO_2NH_4–Pd/C) afforded mixtures including the hydroxylamine[13] and hydrocarbon.[12] $NiCl_2$–$NaBH_4$, $FeCl_2$–HOAc, $TiCl_4$–$LiAlH_4$, $Na_2S_2O_4$, and Ni(OAc)$_2$–BER provided mainly recovered **12**, and Al/Hg reduction (THF–H_2O or CH_3OH–H_2O 8:1, 25 °C) afforded a mixture including the hydroxylamine and the amino alcohol[14] resulting from the additional ketone reduction of **4**.

The use of **4** in eliciting a monoclonal antibody capable of catalyzing the syn elimination of **1** to the disfavored cis olefin **3** is described elsewhere.[3] Its use as well as that of **12** in the generation of catalytic antibodies for additional reactions including the Diels–Alder and aldol reactions are in progress and will be reported in due course.

Experimental Section

(1*S,2*R**,3*S**,4*R**)-2-Benzoyl-2-nitro-3-phenylbicyclo[2.2.1]-hept-5-ene (9).** A solution of (*E*)-α-nitrochalcone[7] (**7**, 5.35 g, 21.1 mmol) in a minimum amount of CH_2Cl_2 (2–3 mL) was treated with freshly cracked cyclopentadiene (**8**, 15.7 mL, 190 mmol, 9.0 equiv). The reaction mixture was stirred at 45 °C for 24 h before the mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 5 × 15 cm, 5% Et_2O–hexane eluant) afforded **9** (5.45 g, 6.73 g theoretical, 81%) as a white crystalline solid: mp 119–120 °C (Et_2O–hexane, colorless needles); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33 (d, 2H, *J* = 8.0 Hz), 7.25–6.97 (m, 8H), 6.72 (m, 1H, C6-H), 5.99 (m, 1H, C5-H), 4.24 (d, 1H, *J* = 2.7 Hz, C3-H), 3.84 (s, 1H, C1-H), 2.93 (s, 1H, C4-H), 2.65 (d, 1H, *J* = 9.8 Hz, C7-H *syn* to ketone), 1.86 (d, 1H, *J* = 9.9 Hz, C7-H *anti* to ketone); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 192.5, 144.3, 137.9, 134.2, 133.7, 133.0, 129.0, 128.6, 128.4, 127.9, 127.5, 105.4, 54.8, 53.5, 51.1, 48.5; IR (neat) ν_{max} 3004, 2970, 1685, 1540, 1465, 1354, 1240 cm^{-1}; FABHRMS (NBA–NaI) *m*/*e* 342.1101 ($C_{20}H_{17}NO_3$ + Na^+ requires 342.1106).[15]

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 74.85; H, 5.29; N, 4.55.

(1*R,2*S**,4*R**,5*S**,6*S**)-6-Benzoyl-2-hydroxy-6-nitro-5-phenylbicyclo[2.2.1]heptane (10).** A solution of **9** (2.20 g, 6.90 mmol) in THF (18 mL, 0.38 M) was treated with 9-BBN (8.62 mmol, 1.25 equiv) in THF (17.25 mL, 0.5 M) and the mixture was allowed to stir at 25 °C under N_2 for 10 h. The resulting mixture was treated successively with 4.15 mL of EtOH, 1.5 mL of 20% aqueous NaOH, and 1.65 mL of 50% aqueous H_2O_2. The reaction solution was warmed at 50 °C for 1 h, recooled to 25 °C, and partitioned between EtOAc (200 mL) and H_2O (200 mL). The EtOAc layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (SiO_2, 5 × 15 cm, 10–25% EtOAc–hexane gradient elution) afforded the major isomer **10** (1.29 g, 55.5%; R_f = 0.32, 20% EtOAc–hexane) and **11** (1*S**,2*R**,4*S**,5*R**,6*S**-5-benzoyl-2-hydroxy-5-nitro-6-phenylbicyclo-[2.2.1]heptane, 400 mg, 17.2%; R_f = 0.26, 20% EtOAc–hexane) as white solids cleanly separated from one another in a 3.2:1 ratio (1.69 g total, 2.32 g theoretical, 73%). For **10**: mp 168–169 °C (EtOAc–hexane, colorless needles); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.38 (d, 2H, *J* = 8.2 Hz), 7.31–6.94 (m, 8H), 4.33 (d, 1H, *J* = 2.4 Hz, C5-H), 3.85 (d, 1H, *J* = 6.8, C2-H), 3.29 (s, 1H, C1-H), 2.63 (d, *J* = 11.3 Hz, C7-H *syn* to ketone), 2.46 (d, 1H, *J* = 4.3 Hz, C4-H), 2.26–2.16 (m, 2H), 1.67–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 189.9, 138.8, 133.7, 133.0, 128.9, 128.5, 128.3, 127.8, 127.4, 105.0, 69.3, 55.5, 55.4, 44.6, 42.1, 35.7; IR (neat) ν_{max} 3331, 2968, 2900, 1689, 1538, 1444, 1353, 1234, 1096, 1063 cm^{-1}; FABHRMS (NBA–NaI) *m*/*e* 360.1230 ($C_{20}H_{19}NO_4$ + Na^+ requires 360.1212).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.13; H, 5.89; N, 4.10.

For **11**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 (d, 2H, *J* = 8.0 Hz), 7.25–6.90 (m, 8H), 4.18 (m, 2H), 3.25 (m, 1H), 2.62 (d, 1H, *J* = 11.2 Hz), 2.26 (s, 1H), 2.12 (d, 1H, *J* = 11.4 Hz), 1.80–1.62 (m, 2H), 1.45 (m, 1H); FABHRMS (NBA–CsI) *m*/*e* 470.0368 ($C_{20}H_{19}NO_4$ + Cs^+ requires 470.0368).

(1*R,2*S**,4*R**,5*S**,6*S**)-6-Benzoyl-6-nitro-5-phenylbicyclo-[2.2.1]heptan-2-yl Hemisuccinate (12).** A solution of **10** (950 mg, 2.82 mmol, 1.0 equiv) in CH_2Cl_2 (9.4 mL, 0.3 M) was treated sequentially with succinic anhydride (564 mg, 5.64 mmol, 2.0 equiv), Et_3N (0.786 mL, 5.64 mmol, 2.0 equiv), and DMAP (95 mg, 0.1 wt equiv), and the reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL) and the organic layer was washed with aqueous 1 N HCl (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 5 × 15 cm, 0–5% CH_3OH–CH_2Cl_2 gradient elution) afforded **12** as a colorless foam (1.20 g, 1.23 g theoretical, 97%): mp 172–173 °C (EtOAc–hexane, colorless needles); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.38 (d, 2H, *J* = 9.5 Hz), 7.31–6.95 (m, 8H), 4.67 (d, 1H, *J* = 6.7 Hz, C2-H), 4.39 (d, 1H, *J* = 2.4 Hz, C5-H), 3.45 (s, 1H, C1-H), 2.74–2.60 (m, 5H), 2.49 (d, 1H, *J* = 3.1 Hz, C4-H), 2.33 (m, 1H, C3-H), 2.12 (d, 1H, *J* = 11.5 Hz, C7-H *anti* to ketone), 1.73 (dd, 1H, *J* = 9.8, 2.2 Hz, C3-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 189.5, 178.0, 171.1, 138.5, 133.6, 133.1, 128.9, 128.6, 128.4, 127.9, 127.6, 104.5, 72.8, 55.6, 52.6, 44.6, 40.4, 36.7, 28.9, 28.8; IR (neat) ν_{max} 3500–2600 (br, CO_2H), 2974, 1738, 1717, 1691, 1542, 1443, 1351, 1256, 1231, 1165 cm^{-1}; FABHRMS (NBA) *m*/*e* 438.1550 ($C_{24}H_{23}NO_7$ + H^+ requires 438.1553).

Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 65.78; H, 5.19; N, 3.02.

A single-crystal X-ray structure determination[11] of **12** was conducted on colorless needles grown from EtOAc–hexane.

(1*R,2*S**,4*R**,5*S**,6*S**)-6-Amino-6-benzoyl-5-phenylbicyclo-[2.2.1]heptan-2-yl Hemisuccinate (4).** A solution of **12** (269 mg, 0.616 mmol) in CH_3OH (9 mL, 0.07 M) was warmed at 45 °C. The reaction solution was treated with Raney Ni (50% slurry in H_2O, 100 mg) and allowed to stir at 45 °C for 20 h under a H_2 atmosphere. The Raney Ni was removed by filtration through Celite and washed successively with CH_3OH (3 × 10 mL) and THF (3 × 10 mL). The combined organic phase was concentrated under pressure. Chromatography (SiO_2, 3 × 15 cm, 1–3% CH_3OH–CH_2Cl_2 gradient elution) afforded **4** as a white foam (74 mg, 250 mg theoretical, 30%): mp 78–82 °C (CH_2Cl_2, white plates); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.33 (d, 2H, *J* = 7.4 Hz), 7.27–7.01 (m, 8H), 5.56 (d, 1H, *J* = 6.2 Hz, C2-H), 5.05 (br s, 2H, NH_2), 2.93 (s, 1H, C5-H), 2.89 (s, 1H, C1-H), 2.66 (m, 4H), 2.44 (d, 1H, *J* = 11.2 Hz, C7-H *syn* to ketone), 2.35 (d, 1H, *J* = 3.2 Hz, C4-H), 2.22 (m, 1H, C3-H), 1.90 (d, 1H, *J* = 11.1 Hz, C7-H *anti* to ketone), 1.73 (dd, 1H, *J* = 13.7, 3.3 Hz, C3-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 202.8, 177.3, 172.2, 142.0, 136.5, 131.1, 129.2, 128.8, 128.4, 127.6, 126.7, 74.1, 72.0, 64.0, 51.1, 45.1, 40.5, 36.0, 29.7, 29.4; IR (neat) ν_{max} 3509, 3500–2600 (br, CO_2H), 2962, 2924, 2854, 1722, 1684, 1263, 1231, 1165 cm^{-1}; FABHRMS (NBA) *m*/*e* 408.1813 ($C_{24}H_{25}NO_5$ + H^+ requires 408.1811).

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.58; H, 6.41; N, 3.66.

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(12) Reactions performed on **12**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.95 (d, 2H, *J* = 7.5 Hz), 7.58–7.15 (m, 8H), 4.70 (d, 1H, *J* = 7.5 Hz), 3.82 (t, 1H, *J* = 5.0 Hz), 3.56 (d, 1H, *J* = 5.0 Hz), 2.82 (d, 1H, *J* = 2.5 Hz), 2.69 (d, 1H, *J* = 2.5 Hz), 2.65–2.45 (m, 4H), 2.22 (m, 1H), 1.98 (d, 1H, *J* = 10.0 Hz), 1.85 (d, 1H, *J* = 10.0 Hz), 1.60 (m, 1H); FABMS (NBA–CsI) *m*/*e* 525 ($C_{24}H_{24}O_5$ + Cs^+ requires 525).

(13) Reactions performed on **12**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.30–7.05 (m, 10H), 6.40–6.10 (br s), 5.64 (d, 1H, *J* = 7.5 Hz), 3.18 (s, 1H), 2.82–2.63 (m, 5H), 2.46–2.31 (m, 2H), 2.12 (m, 1H), 1.92 (d, 1H, *J* = 10.0 Hz), 1.78 (m, 1H); FABMS (NBA) *m*/*e* 424 ($C_{24}H_{25}NO_6$ + H^+ requires 424).

(14) Reaction performed on **10**: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.45–7.18 (m, 10H), 4.57 (s, 1H), 4.45 (d, 1H, *J* = 7.5 Hz), 2.52–2.47 (m, 2H), 2.39 (d, 1H, *J* = 10.0 Hz), 2.10–1.84 (br m), 1.68 (s, 1H), 1.47 (m, 1H); FABHRMS (NBA) *m*/*e* 310.1802 ($C_{20}H_{23}NO_2$ + H^+ requires 310.1807).

(15) A mixture of minor diastereomers (<3%) was isolated in trace amounts.