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An intramolecular oxo Diels–Alder approach to 1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl esters

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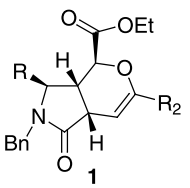
Abstract—The diastereoselective synthesis of a series of 1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl esters via an oxo Diels–Alder reaction is described. Ab initio calculations predicted the products of the *exo* cycloaddition to be the thermodynamic products while the products resulting from the *endo* cycloaddition were predicted to be the kinetic products. The calculations were born out by experimental data.

1. Introduction

The synthesis of functionalized pyrrolidine templates is a good entry point to the synthesis of peptidomimetic libraries.[1] We recently communicated the synthesis of a series densely functionalized pyrrolidines **1** using the intramolecular oxo Diels–Alder reaction.[2,3] These Diels–Alder reactions allowed for the control of facial selectivity, and complete *exo* selectivity affording the *cis* fused 5,6 system **1**. Our previous work on analogous carbon Diels–Alder reactions afforded *endo* selective reactions which yielded a *trans* ring junction in our 5,6 systems. As in all previous studies the oxo case proceeded with complete facial selectivity.[4] The selectivity is derived from the R group on the carbon alpha to the amino group initially originating from the alpha amino acid precursor. The complete *exo* selectivity of this reaction was intriguing and led us to further examine this system. We initially decided to carry out ab initio calculations on this Diels–Alder reaction.



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While experimentally we observed that the intramolecular Diels–Alder reaction of these trienes proceeded with complete *exo*-selectivity to give the *cis*-fused pyrrolidinone templates, calculations[5] at the B3LYP/6-31G(d)//B3LYP/6-31G(d) level of theory[6] suggested that the *trans* isomers **2** and **3** are the kinetic products of the reaction and the *cis* isomer **4** can be formed via an isomerization of the *trans* isomers. The activation energies leading to the *trans* isomers **2** and **3** are 24.3 and 24.9 kcal/mol, respectively, while those for the *cis* isomers **4** and **5** are both 28.4 kcal/mol. The calculated heats of reaction leading to **2** and **3** are −9.3 and −9.1 kcal/mol, respectively, while those for **4** and **5** are −17.4 and −14.7 kcal/mol (Fig. 1). While the calculations agree with our observations and predict that the observed *cis* product **4** is the thermodynamic product, we felt it would be reasonable to try to isolate a kinetic product.

The intermediate triene **7** was synthesized as described previously (Scheme 1).[2] We then carried out the intramolecular Diels–Alder reactions of **7a-j** at reflux in benzene. Previously reflux of **7a-j** in toluene produced only **9a-j** with the *cis* ring juncture shown. The compounds resulting from (**7a-j**) reflux in benzene **8a-j**, had the *trans* fused ring juncture (Fig. 2). Both reactions proceed with complete facial selectivity. The phenylalanine derivatives **8** proceeded smoothly to the *trans* fused products but decomposed at room temperature over time depending on the substitution pattern. As **8a-j** are predicted to be the kinetic products, we attempted to convert the isolated *trans* products **8a-j** to the proposed thermodynamic products **9a-j** by refluxing them in toluene. We were not able to directly convert **8** to **9** in the cases attempted. Once isolated the

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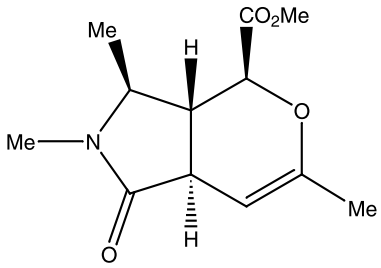

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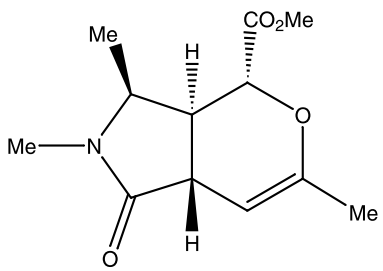

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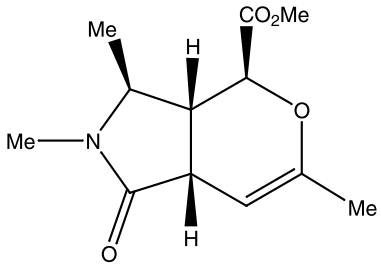

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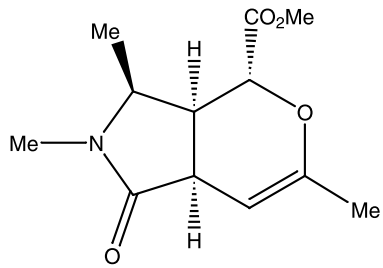

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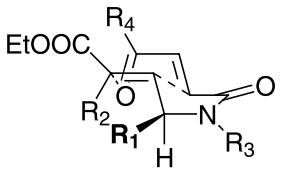

Endo / equatorial

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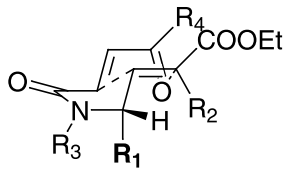

Endo / axial

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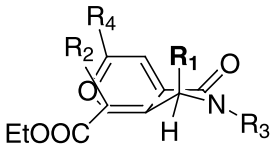

Exo / axial

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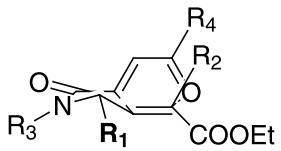


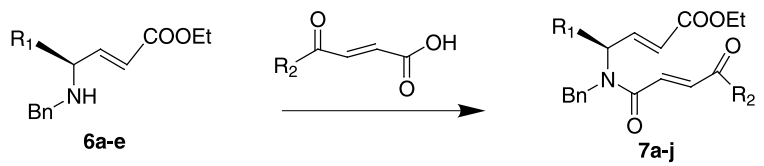
Exo / equatorial

5

Figure 1.

compounds are relatively labile to an undetermined oxidative decomposition mechanism which bleeds off product. These compounds **8a**-**j**, however, could be stored in benzene under argon at −20°C.

NOE, HMBC, HMQC and HETCOR experiments were utilized to prove the stereochemistry of the isomers in each case. With 2 ring juncture isomers of each template in hand, structural assignments were made based on two-dimensional NMR experiments. COSY experiments were used to locate the position of different protons as previously described.[2] The resolution in deuterated chloroform was not satisfactory in all cases so the NMR studies were carried out in deuterated acetonitrile or toluene to further resolve

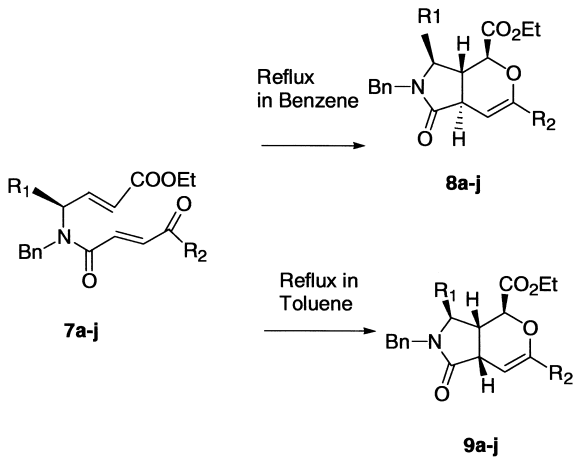


6 a. R_1=Bn
6 b. R_1= iPr
6 c. R_1=(COOBn)CH_2
6 d. R_1=CH_3
6 e. R_1=3-N-Benzylindole

7a. R_1=Bn, R_2= CH_3
7b. R_1=Bn, R_2=Ph
7c. R_1 =iPr, R_2=CH_3
7d. R_1=iPr, R_2=Ph
7e. R_1=(COOBn)CH_2, R_2=CH_3

7f. R_1=(COOBn)CH_2, R_2=Ph
7g.R_1= CH_3, R_2=Ph
7h. R_1=3-N-Benzylindole, R_2=CH_3

Scheme 1.



Compound	R1	R2	Yield 8	Yield 9
a	Bn	CH_3	87%	91 %
b	Bn	Ph	78%	85%
c	iPr	CH_3	81%	87 %
d	iPr	Ph	70%	77%
e	CH_2 (CO_2Bn)	CH_3	66%	72%
f	CH_2 (CO_2Bn)	Ph	49%	48%
g	CH_3	Ph	78%	82%
h	3-N-Benzylindolyl	CH_3	66%	72%

Figure 2.

adjacent peaks. A series of NOESY experiments followed by HMBC and HMQC were then performed.

The NOE studies are best exemplified by comparing **8d** to **9d** (Fig. 3). In **8d** there is a strong NOE between H6 to H3 indicating they are on the same face of the molecule. There is no observable NOE between H4 and H3. There is a NOE between H3 and H5 again indicating they are on the same face and finally there is no observable NOE between H4 and H5. This data is consistent with the relative stereochemistry shown in structure **1**.[7] We irradiated structure **9d** and found a strong NOE between H4 and H3 indicating they are on the same face of the molecule. We were unable to resolve H5 and H3 enough to irradiate either peak. Finally we observed a strong NOE between H6 and H5. This again is consistent with the relative stereochemistry shown in structure **9d**. With this data in hand the rest of the compounds could be assigned by comparison of coupling constants.

We believe that we have demonstrated that the *trans* fused products of the oxo Diels–Alder reaction in question are the kinetic products of the reaction. While the products themselves are interesting it is clear that any analogs of these compounds will be more difficult to handle than the *cis* fused products. This may limit the utility of the *trans* fused compounds as inputs for library generation.

2. Experimental

2.1. General methods

All reactions were carried out in an atmosphere of dry nitrogen at room temperature unless otherwise stated. Reaction temperatures other than room temperature were recorded as bath temperature unless otherwise stated. ^{1}H NMR and ^{13}C NMR were recorded on 300, 400 MHz spectrometers (300 or 400 MHz ^{1}H NMR, respectively, and 75 or 100 MHz ^{13}C NMR, respectively) in deuteriochloroform ($CDCl_3$) with chloroform (d 7.26 ppm ^{1}H, d 77 ppm ^{13}C) as the internal standard unless otherwise stated. All non-aqueous reactions were carried out in an atmosphere of dry nitrogen at room temperature unless otherwise stated. All solvents were purchased from commercial sources and were used without further purification. TLC were performed on glass baked plates coated with silica gel 60 with an F 254 indicator. The chromatograms were visualized under UV light and/or by staining with phosphomolybdic acid (20% solution in ethanol). Flash column chromatography was performed with 40–60 mm silica gel (Merck).

2.2. Procedure for chiral HPLC

The enantiomeric purity of the compounds **6a-e** checked by comparing with corresponding racemic compounds via chiral HPLC separation techniques using the following conditions: Instrument: Agilent Technologies 1100 series. Solvent system: 0.1% TEA/MeOH, column: Chiralcel AD-RH, flow rate of 1 mL/min. Retention time for racemic

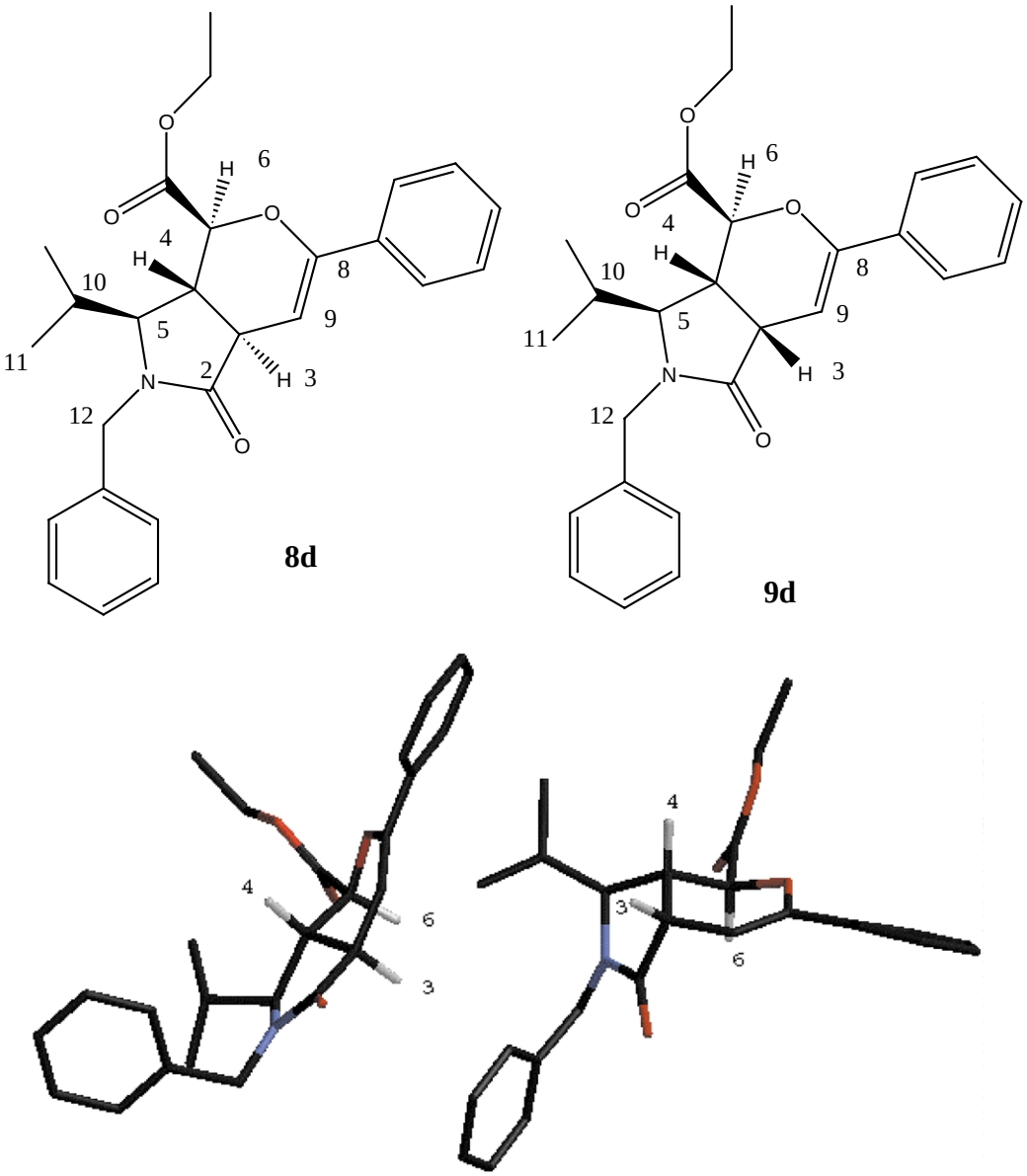


Figure 3.

compound: 4.056 and 4.421 min. The retention time for the L-amino acid derived compound 4.413 min. Back pressure: 22 bar.

2.3. LC/MS conditions

The LC/MS data were collected by using the following conditions: solvents are A: H_2O+0.5% TFA, B: CH_3CN+0.5% TFA, The gradient method was 5–100% B over 3.7 min, hold at 100% B for 0.5 min. Return to 5% B over 0.4 min. The total runtime is 4.6 min. The flow rate is 0.450 mL/min. Column: Zorabax Bonus-RP 5 μm 2.1×50 mm. Instrument: Agilent technologies: 1100 LC/MSD using ESI.

2.4. General procedure for preparation of amino acid derived *N*-Bn protected unsaturated esters: 4-benzyl amino-5 phenyl-pent-2-enoic acid ethyl ester 6a

To a solution of the Boc-protected phenylalanine ester (3.5 g, 10.9 mmol) was added 25 mL of TFA in CH_2Cl_2 (1:1) at 0°C and stirred at room temperature for 30 min. The excess methylene chloride and TFA was evaporated by solvent exchange with chloroform (4 iterations). The compound was then dissolved in dry methylene chloride again (50 mL) and cooled to 0°C. BnBr (2.8 g, 16.4 mmol) and $CsCO_3$ (10.7 g, 32.91 mmol) was added. The solution was stirred for 12 h while slowly warming to room temperature. The reaction mixture was then again cooled to 0°C and ice-cold water (150 mL) was added. The reaction mixture was then extracted with methylene chloride (3×50 mL). The combined organic layers were washed with brine, dried over $NaSO_4$ and filtered. The solvent was then removed. Flash chromatography using a gradient of 10–20% EtOAc/hexane gave the desired compound (2.7 g, 81%) as an oily liquid. ^{1}H NMR δ: 1.26 (t, J=7.2 Hz, 3H), 2.79 (ABX, J=5.7, 12 Hz, 2H), 3.47 (m, J=6.3 Hz, 1H), 3.56 (AB, J=13.8 Hz, 2H), 4.18 (m, J=7.2 Hz, 2H), 5.90 (d, J=15 Hz, 1H), 6.86 (dd, J=15.6, 7.5 Hz, 1H), 7.27 (m, 10H).

^{13}C NMR, (75 MHz, $CDCl_3$) δ: 21.4, 42, 51.7, 60.1, 60.7, 122.5, 127.3, 128.3, 128.7, 128.9, 129.7, 140.3, 150.5, 166.7. LC/MS calculated for $C_{20}H_{23}NO_2$ (MH^+): 310, found 310.

2.5. General procedure for the preparation of amino acid derived trienes

2.5.1. 4-[Benzyl-(4-oxo-pent-2-enoyl)-amino]-5-phenyl-pent-2-enoic acid ethyl ester 7a. To a stirred solution of the *N*-benzyl protected unsaturated ester (0.167 g,.54 mmol) in dry DMF (15 mL), was added at 0°C (.31 g, 1.63 mmol) EDCI, followed by HOAT (.22 g, 1.63 mmol), and 3-acetyl acrylic acid (.185 g, 1.63 mmol). The reaction mixture was stirred overnight (14 h) slowly warming from 0°C to room temperature. The reaction mixture was then quenched with ice-cold water (100 mL) and was extracted with diethyl ether (3×50 mL). The combined ether layer was washed with water (3×20 mL) and saturated brine solution (1×20 mL). The organic layer was then dried over $NaSO_4$ and concentrated under vacuum to give a yellow liquid. On chromatography using 20–40% EtOAc/hexane a pure compound was isolated (.182 g) in 82% yield as a yellow foam.

^{1}H NMR δ: 1.12 (t, J=7.24 Hz, 3H), 2.21 (s, 3H), 2.85–3.25 (m, 2H), 4.05 (q, J=7.24 Hz), 4.10–4.50 (AB, J=18.6 Hz), 4.85 (m, 1H), 5.65 (d, J=14.26 Hz, 1H), 6.53–7.35 (m, 12H). ^{13}C NMR δ: ($CDCl_3$): 21.4, 29.3, 38.1, 50.9, 59.8, 60.7, 61.1, 123.6, 123.8, 127, 127.2, 127.6, 127.9, 128.3, 128.8, 129.0, 129.4, 132.2, 136.7, 138.5, 144.9, 165.6, 166.9, 197.7. LC/MS calculated for: $C_{25}H_{27}NO_4$ (MH^+) 406.2018, found 406.2027.

2.5.2. 4[Benzyl-(4-oxo-4-phenyl-but-2amino]-5-phenyl-pent-2-enoic acid ethyl ester 7b. To the chilled solution (0°C) of *N*-benzyl ester (0.247 g, 0.79 mmol) dissolved in dry DMF (20 mL) was added EDCI (0.53 g, 2.79 mmol), followed by HOAT (0.37 g, 2.79 mmol), and 3-benzyl acrylic acid (0.49 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 19 h. Then the reaction mixture was again cooled down to 0°C and 100 mL water was added. The crude reaction mixture was then extracted with diethyl ether (3×25 mL). The combined organic layer was further washed with water again followed by brine. It was dried over $NaSO_4$ and solvent was removed in vacuo. The crude compound was then used immediately in next step to carry out the cyclization. LC–MS calculated for: $C_{30}H_{29}NO_4$ (MH^+) 468, found 468.

2.5.3. 4[Benzyl-(4-oxo-4-phenyl-pent-2-enoyl)-amino]-5-methylhex-2-enoic acid ethyl ester 7c. The title compound was prepared as described for **7b** and was isolated in 81% yield as a yellow oil. ^{1}H NMR: 0.80 (d, 3H, J=5.07 Hz), 0.85 (d, 3H, J=5.21 Hz), 1.15 (t, 3H, J=7.15 Hz), 1.97 (s, 3H), 2.01 (m, 1H), 2.55 (dd, 1H, J=8.55, 2.11 Hz), 3.11 (m, 1H), 3.25 (m, 1H), 3.80 (d, 1H, J=9.56 Hz), 3.86 (d, J=14.82 Hz), 4.25 (m, 2H, J=7.15 Hz), 4.99 (d, 1H, J=4.39 Hz), 5.11 (d, 1H, J=14.81 Hz), 7.15–7.41 (m, 5H). ^{13}C NMR: 16.1, 18.7, 20.0, 28.5, 33.1, 39.1, 44.6, 61.7, 61.8, 75.4, 95.0, 128.0, 128.6, 129.1, 130.2, 136.3, 152.4, 169.9, 174.1. HRMS calculated for: $C_{21}H_{27}NO_4$ (MH^+) 358.2018, found 358. 1999.

2.5.4. 4[Benzyl-(4-oxo-4-phenyl-but-2-enoyl)amino]-5-methylhex-2-enoic acid ethyl ester 7d. The title compound was isolated in 72% yield as a yellow oil. ^{1}H NMR: 0.82 (d, 3H, J=7.3 Hz), 0.90 (d, 3H, J=7.25 Hz), 1.30 (t, 3H, J=7.25 Hz), 1.98–2.15 (m, 1H, J=7.1 Hz), 2.45 (dd, 1H, J=10.2, 2.5 Hz), 3.05 (dd, 1H, J=2.8, 12.6 Hz), 3.45 (dd, 1H, J=2.24, 9.6 Hz), 3.95 (d, 1H, J=15.5 Hz), 4.15–4.38 (m, 2H), 4.70 (d, J=10.9 Hz), 5.30 (d, 1H, J=15.43 Hz), 6.05 (d, J=2.9 Hz), 7.05–7.65 (m, 10H). ^{13}C NMR: 17.3, 27.1, 40.6, 42.6, 44.5, 61.6, 63.8, 79.4, 96.5, 124.7, 127.5, 127.7, 128.2, 128.5, 134.4, 136.4, 151.7, 169.7, 172.9. HRMS calculated for: $C_{26}H_{29}NO_4$ (MH^+) 420.2175, found 420.2183.

2.5.5. (3*S*,3a*R*,4*S*,7a*R*) 2,3-Dibenzyl-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9a. The triene (0.181 g, 0.45 mmol) was dissolved in dry toluene (8 mL). The reaction mixture was refluxed for 16 h. The residual toluene was then removed in vacuo. The title compound was isolated by eluting with 10–20% EtOAc/CH_2Cl_2. to afford a yellow foam (0.164 g, 0.40 mmol), yield 91%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, J=7.14 Hz, 3H), 1.85 (s, 3H), 2.48 (ddd, J=3.41, 8.6 Hz, 1H), 2.65 (m, J=13.82, 3.41 Hz, 1H), 2.85 (m, 1H), 3.05 (dd, J=13.82, 4.27 Hz, 1H), 3.52 (m, 2H), 3.95 (q, J=7.16 Hz, 2H), 4.01 (d, J=14.82 Hz, 1H), 4.85 (d, J=4.27 Hz, 1H), 5.15 (d, J=14.82 Hz, 1H), 7.01–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 14.3, 20.1, 37.5, 37.8, 38.7, 44.9, 58.2, 61.8, 73.8, 94.4, 127.5, 128.2, 128.6, 129.2, 129.3, 129.6, 136.3, 136.6, 152.3, 169.6, 174.1. HRMS calculated for: $C_{25}H_{27}NO_4$ $(MH)^+$ 406.2018, found 406.2018; $[\alpha]_D^{20}$=+58 (*c* 0.10, $CHCl_3$).

2.5.6. (3*S*,3a*R*,4*S*,7a*S*) 2,3-Dibenzyl-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8a. The triene (0.158 g, 0.39 mmol) was dissolved in dry benzene (8 mL). The reaction mixture was refluxed for 7 h. The residual benzene was then removed in vacuo. The title compound was isolated by eluting with 10–20% EtOAc/CH_2Cl_2 to afford a yellow oil (0.137 g, 0.34 mm) yield 87%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, J=7.10 Hz, 3H), 1.68 (s, 3H), 2.10 (m, J=3.41, 10.58 Hz, 1H), 2.65 (m, J=13.82, 3.41 Hz, 1H), 2.85 (m, 1H), 3.05 (dd, J=10.82, 4.27 Hz, 1H), 3.52 (m, 2H), 3.00–3.25 (m, 2H), 3.90 (d, J=13.90 Hz, 1H), 4.05 (m, 2H), 4.25 (m, 1H), 5.05 (d, J=13.9 Hz, 1H), 5.75 (d, J=10.57 Hz, 1H), 6.56–8.51 (m, 10H, J=7.16 , 2H), 4.01 (d, J=14.82 Hz, 1H), 4.85 (d, J=4.27 Hz, 1H), 5.15 (d, J=14.82 Hz, 1H), 7.01–7.42 (m, 10H). HRMS calculated for: $C_{25}H_{27}NO_4$ $(MH)^+$ 406.2018, found 406.2006.

2.5.7. (3*S*,3a*R*,4*S*,7a*R*) 2,3-Dibenzyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9b. The crude compound was dissolved in toluene and was refluxed for 16 h to isolate the desired compound after chromatography using 30% EtOAc/hexane, in 85% yield as an off white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.21 (t, J=7.12 Hz, 3H), 2.65 (ddd, J=14.82, 3.41 Hz, 1H), 3.05 (dd, J=7.95, 3.41 Hz, 1H), 3.35 (m, J=14.82, 3.62 Hz, 1H), 3.65 (J=7.95, 3.62 Hz, 1H), 3.75 (m, 1H), 4.05–4.30 (m, 3H), 5.11 (d, J=14.94 Hz, 1H), 5.55 (d, J=4.32 Hz, 1H), 7.05–7.70 (m, 15H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 27.6, 37.8, 42.5, 45.6, 53.0,

59.5, 67.9, 69.3, 95.8, 124.0, 125.3, 125.6,125.7, 126.2, 126.8, 126.9, 127.2, 127.5, 132.2, 133.2, 133.5, 152.2, 166.7, 171.7. HRMS calculated for: $C_{30}H_{29}NO_4$ 467.2097 (M^+), found 467.2096; $[\alpha]_D^{20}=-35$ (*c* 0.25, $CHCl_3$).

2.5.8. (3*S*,3a*R*,4*S*,7a*S*) 2,3-Dibenzyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8b. The title compound was prepared as before and was isolated in as a yellow oil in 78% yield. ^{1}H NMR: 1.25 (t, *J*=7.25 Hz, 3H), 2.35 (dd, *J*=8.64, 2.35 Hz, 1H), 2.85 (dd, *J*=8.67, 2.41 Hz, 1H), 3.15 (m, *J*=10.42 Hz, 2H), 4.00 (m, 1H), 4.05 (d, *J*=14.41 Hz, 1H), 4.15–4.45 (m, *J*=7.21 Hz, 2H), 4.90 (d, *J*=10.52 Hz, 1H), 5.13 (d, *J*=14.41 Hz, 1H), 5.95 (m, 1H), 6.85–7.75 (m, 15H). HRMS calculated for: $C_{30}H_{29}NO_4$ 468.2175 (MH^+), found 468.2166.

2.5.9. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-isopropyl-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8c. The title compound was prepared as described for **1b** and was isolated in 81% yield as a beige foam. ^{1}H NMR: 0.81 (d, *J*=7.19 Hz, 3H), 0.91–0.95 (d, *J*=7.16 Hz, 3H), 1.31 (t, *J*=7.16 Hz, 3H), 1.81 (s, 3H), 1.92 (m, *J*=5.60, 7.16 Hz, 1H), 2.31–3.42 (m, *J*=10.24, 12.45 Hz, 1H), 2.87 (m, *J*=12.48 Hz, 1H), 3.35 (d, *J*=9.87 Hz), 1H), 3.89 (d, *J*=15.03 Hz, 1H), 4.05–4.35 (m, 2H), 4.58 (d, *J*=10.59 Hz), 5.16 (s, 1H), 5.18 (d, *J*=15.06 Hz, 1H), 6.99–7.35 (m, 5H). ^{13}C NMR: 15.2, 18.0, 19.2, 20.7, 28.6, 41.8, 43.7, 45.9, 62.8, 64.5, 80.3, 96.0, 128.7, 129.9, 129.2, 130.0, 130.2, 137.7, 152.6, 171.2. HRMS calculated for: $C_{21}H_{27}NO_4$ $(MH)^+$ 358.2018, found 358.2022.

2.5.10. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-isopropyl-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9c. The title compound was prepared as described for **1b** and was isolated in 87% yield as an off white foam. ^{1}H NMR: 0.80 (d, 3H, *J*=7.20 Hz, 3H), 0.85 (d, *J*=7.20 Hz, 3H), 1.15 (t, *J*=7.15 Hz, 3H), 1.97 (s, 3H), 2.02 (m, 1H), 2.55 (dd, *J*=8.42, 2.0 Hz, 1H), 3.11 (m, 1H), 3.25 (m, 1H), 3.80 (d, *J*=8.45 Hz, 1H), 3.86 (d, *J*=15.5 Hz, 1H), 4.25 (m, 2H), 4.99 (d, 1H, *J*=2.9 Hz, 1H), 5.11 (d, *J*=15.50 Hz, 1H), 7.15–7.41 (m, 5H). ^{13}C NMR: 16.1, 18.7, 20.0, 28.5, 33.1, 39.1, 44.6, 61.7, 61.8, 75.4, 95.0, 128.0, 128.6, 129.1, 130.2, 136.3, 152.4, 169.9, 174.1. HRMS calculated for $C_{21}H_{27}NO_4$: $(MH)^+$ 358.2018, found 358.2005.

2.5.11. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-isopropyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8d. The title compound was prepared as described for **1b** and was isolated as an off white foam in 70% yield. ^{1}H NMR: 0.82 (d, *J*=7.20 Hz, 3H), 0.90 (d, *J*=7.25 Hz, 3H), 1.98–2.15 (m, *J*=2.0, 7.12 Hz, 1H), 2.45 (dd, *J*=10.2, 2.01 Hz, 1H), 3.05 (dd, *J*=2.8, 12.6 Hz, 1H), 3.45 (dd, *J*=2.2, 9.6 Hz, 1H), 3.95 (d, *J*=15.5 Hz, 1H), 4.15–4.38 (m, 2H), 4.70 (d, *J*=10.90 Hz, 1H), 5.30 (d, *J*=15.3 Hz, 1H), 6.05 (d, *J*=2.9 Hz, 1H), 7.05–7.65 (m, 10H). ^{13}C NMR: 17.3, 27.1, 40.6, 42.6, 44.5, 61.6, 63.8, 79.4, 96.5, 124.7, 127.5, 127.7, 128.2, 128.5, 128.7, 128.8, 134.3, 136.4, 151.7, 169.7, 172.9. HRMS calculated for: $C_{26}H_{29}NO_4$ $(MH)^+$ 420.2175, found: 420.2191.

2.5.12. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-isopropyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9d. The title compound was prepared as described for **1b** and was isolated as a yellow oil in 77% yield. ^{1}H NMR: 0.87 (dd, *J*=7.10, 6.93 Hz, 6H), 1.18 (t, *J*=7.14 Hz, 3H), 2.11 (m, 1H), 2.70 (dd, *J*=2.70, 8.43, 1 Hz), 3.31 (m, 2H), 3.85 (d, *J*=14.81 Hz, 1H), 4.00 (d, *J*=8.76 Hz, 1H), 4.15 (q, *J*=7.12 Hz, H), 5.11 (d, *J*=14.88 Hz, 1H), 5.81 (d, *J*=4.47 Hz, 1H), 7.18–7.64 (m, 5H). ^{13}C NMR: 15.6, 18.4, 28.1, 33.4, 39.4, 44.3, 61.3, 61.6, 75.5, 96.0, 125.0, 127.7, 128.1, 128.2, 128.7, 134.2, 135.8, 152.4, 169.4, 173.3. HRMS calculated for: $C_{26}H_{29}NO_4$ $(MH)^+$ 420.2175, found: 420.2174.

2.5.13. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-(1-benzyl-1*H*-indol-3-ylmethyl)-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8e. The title compound was isolated as a yellow gum in 66% yield. ^{1}H NMR: 0.99 (t, *J*=7.24 Hz, 3H), 2.42 (AB, *J*=5.45, 10.55 Hz, 1H), 3.05 (ABX, *J*=14.6 Hz, 1H), 3.98 (q, *J*=7.24 Hz, 2H), 4.65 (d, *J*=15.82 Hz, 1H), 4.92 (d, *J*=15.82 Hz, 1H), 7.02–7.65 (m, 14H). HRMS calculated for: $C_{34}H_{34}NO_4$ $(MH)^+$ 535.2597, found: 535.2566.

2.5.14. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-(1-benzyl-1*H*-indol-3-ylmethyl)-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9e. The title compound was isolated as a yellow foam in 72% yield. ^{1}H NMR: 0.99 (t, *J*=7.24 Hz, 3H), 1;.82 (s, 3H), 2.42 (AB, *J*=5.45, 10.55 Hz, 1H), 3.75 (ABX, *J*=14.6 Hz, 1H), 3.99 (q, *J*=7.24 Hz, 2H), 4.75 (d, *J*=15.82 Hz, 1H), 4.97 (d, *J*=15.82 Hz, 1H), 5.20 (s, 2H), 7.02–7.65 (m, 14H). HRMS calculated for: $C_{34}H_{34}NO_4$ $(MH)^+$ 535.2597, found: 535.2606.

2.5.15. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-benzyloxycarbonyl-methyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8f. The title compound was isolated as a yellow oil in 49% yields. ^{1}H NMR: 1.32 (m, *J*=7.21 Hz, 3H), 2.30–2.55 (m, 2H), 3.05–3.25 (m, *J*=12.76 Hz, 1H), 3.85 (m, *J*=12.65 Hz, 1H), 4.00–4.25 (m, 2H), 4.70–5.00 (m, 2H), 5.85 (m, 1H), 5.89 (m, 1H), 6.99–7.68 (m, 10H). HRMS calculated for: $C_{32}H_{31}NO_6$ $(MH)^+$ 526.2229, found 526.2220.

2.5.16. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-benzyloxycarbonyl-methyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9f. The title compound was isolated as a yellow foam in 48% yields. ^{1}H NMR: 1.52 (m, *J*=7.20 Hz, 3H), 2.52 (dd, 1H, *J*=4.45 Hz, 1H), 2.81 (dd, *J*=4.10 Hz, 1H), 2.85 (m, 1H), 3.35 (m, 1H), 3.85 (m, 1H), 3.99 (d, *J*=15.2 Hz, 1H), 4.25 (m, 2H), 4.95 (d, *J*=15.2 Hz, 1H), 5.05 (s, 2H), 5.75 (d, *J*=4.21 Hz, 1H), 7.02–7.75 (m, 15H). ^{13}C NMR: 37.0, 38.1, 38.6, 44.5, 54.3, 61.7, 66.9, 73.7, 95.3, 117.0, 122.9, 125.1, 127.8, 127.9, 128.2, 128.5, 128.6, 128.8, 130.5, 133.4, 134.2, 135.2, 135.7, 152.6, 169.3, 169.9. HRMS calculated for: $C_{32}H_{31}NO_6$ $(MH)^+$ 526.2229, found 526.2231.

2.5.17. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-methyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9g. The title compound was

isolated as a pale yellow oil in 82% yield. ^{1}H NMR: 0.98 (m, 2H), 1.20 (m, 3H), 2.00 (s, 3H), 2.65 (m, 1H), 3.25 (m, 1H), 3.35 (m, 1H), 3.85 (m, 1H), 3.95–4.25 (m, 2H), 4.32 (m, 1H), 4.89 (d, *J*=14.89 Hz, 1H), 5.65 (d, *J*=3.85 Hz), 7.05–7.65 (m, 5H). ^{13}C NMR: 18.1, 22.7, 29.3, 38.1, 41.1, 44.0, 53.0, 61.7, 72.6, 95.3, 125.3, 127.5, 127.7, 134.6, 136.0, 152.3, 169.7, 173.1; HRMS calculated for $C_{24}H_{25}NO_4$ $(MH)^+$ 392.1862, found 392.1857.

2.5.18. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-methyl-1-oxo-6-phenyl-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8g. The title compound was isolated as a yellow oil in 78% yield. ^{1}H NMR: 0.98 (m, 2H), 1.20 (m, 3H), 2.00 (s, 3H), 2.55 (m, 1H), 3.25 (m, 1H), 3.35 (m, 1H), 3.85 (m, 1H), 3.95–4.25 (m, 2H), 4.32 (m, 1H), 4.89 (d, *J*=14.89 Hz, 1H), 5.65 (d, *J*=3.85 Hz), 7.05–7.65 (m, 5H). ^{13}C NMR: 19.3, 30.0, 38.6, 43.5, 44.6, 53.3, 62.07, 72.6, 95.4, 128.0, 128.6, 129.1, 134.9, 137.0, 152.0, 169.8, 171.5. HRMS calculated for $C_{24}H_{25}NO_4$ $(MH)^+$ 392.1862, found 392.1885.

2.5.19. (3*S*,3a*R*,4*S*,7a*S*) 2-Benzyl-3-(1-benzyl-1*H*-indol-3-ylmethyl)-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 8h. The title compound was prepared directly from **6e** without intermediate isolation of 7 h and was isolated in 66% yield as a yellow gum. ^{1}H NMR: 0.99 (t, *J*=7.24 Hz, 3H), 2.42 (AB, *J*=5.45, 10.55 Hz, 1H), 3.05 (ABX, *J*=14.6 Hz, 1H), 3.98 (q, *J*=7.24 Hz, 2H), 4.65 (d, *J*=15.82 Hz, 1H), 4.92 (d, *J*=15.82 Hz, 1H), 7.02–7.65 (m, 14H). HRMS calculated for: $C_{34}H_{34}NO_4$ $(MH)^+$ 535.2597, found: 535.2566.

2.5.20. (3*S*,3a*R*,4*S*,7a*R*) 2-Benzyl-3-(1-benzyl-1*H*-indol-3-ylmethyl)-6-methyl-1-oxo-1,2,3,3a,4,7a-hexahydro-pyrano[3,4-*c*]pyrrole-4-carboxylic acid ethyl ester 9h. The title compound was prepared directly from **6e** without intermediate isolation of 7 h and was isolated in 72% yield as a yellow foam. ^{1}H NMR: 0.99 (t, *J*=7.24 Hz, 3H), 1;.82 (s, 3H), 2.42 (AB, *J*=5.45, 10.55 Hz, 1H), 3.75 (ABX, *J*=14.6 Hz, 1H), 3.99 (q, *J*=7.24 Hz, 2H), 4.75 (d, *J*=15.82 Hz, 1H), 4.97 (d, *J*=15.82 Hz, 1H), 5.20 (s, 2H), 7.02–7.65 (m, 14H). HRMS calculated for; $C_{34}H_{34}NO_4$ $(MH)^+$ 535.2597, found: 535.2606.

References

1. (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. Dessimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Guan, Y.; Green, M. A.; Bergstrom, D. E. *J. Comb. Chem.* **2000**, *2*, 297. and Refs. 2–9 therein. (c) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171. (d) Feng, Z.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1181.
2. Murray, W. V.; Mishra, P. K.; Sun, S.; Maden, A. *Tetrahedron Lett.* **2002**, *43*(41), 7389–7392.
3. For synthesis of 6,5 fused systems via oxo Diels Alder reactions see: Tietz, L. F.; Beifus, U.; Ruthe, M.; Ruhlman, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem. Int. Ed.* **1988**, *27*, 1186–1187.
4. (a) Murray, W. V.; Sun, S.; Turchi, I. J.; Brown, F. K.; Gauthier, A. D. *J. Org. Chem.* **1999**, *64*, 5930. (b) Sun, S.; Turchi, I. J.; Murray, W. V. *J. Org. Chem.* **2000**, *65*, 2555. For synthesis of other hydroisoquinone and hydroisoindole derivatives via Diels–Alder reactios, see: (c) Guitierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335. (d) Moriwake, T.; Hmano, S.; Saito, S.; Torii, S. *J. Org. Chem.* **1989**, *54*, 4114. (e) Martin, S.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170. (f) Guy, A.; Lemaire, M.; Negre, M.; Guette, J. P. *Tetrahedron Lett.* **1985**, *26*, 3575. (g) Takeuchi, H.; Fujimoto, T.; Hshino, K.; Motoyoshia, J.; Kakehi, A.; Yamamoto, I. *J. Org. Chem.* **1998**, *63*, 7172.
5. *Jaguar*; Schrodinger, Inc. 121 SW Morrison, Suite 1212, Portland, OR 97204.
6. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
7. Fujimoto, H.; Hshino, T.; Motoyoshia, K.; Kakehi, J.; Yamamoto, I. *J. Org. Chem.* **1998**, *63*, 7172.