Catalyst and Pressure Dependent Reductive Cyclizations for the Diastereoselective Synthesis of Hexahydropyrrolo[1,2-a]quinoline-5-carboxylic Esters

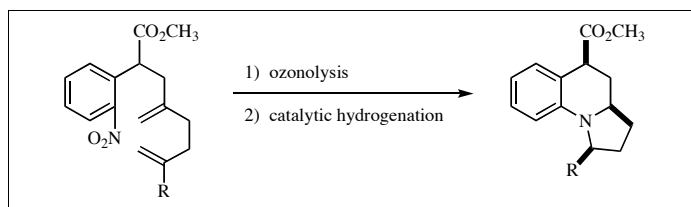Richard A. Bunce*, James E. Schammerhorn [1] and LeGrande M. Slaughter

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A diasteroselective synthesis of 1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-5-carboxylic esters has been developed using a tandem reduction-double reductive amination reaction. The nitro dicarbonyl cyclization substrates were synthesized by alkylation of methyl (2-nitrophenyl)acetate with 2-bromomethyl-1,5-hexadiene derivatives, followed by ozonolysis. Catalytic hydrogenation of each substrate gave the target heterocycle, along with a deacylated product and an adduct resulting from capture of the intermediate hydroxylamine by the side chain carbonyls. The product ratio varied dramatically with the catalyst and the hydrogen pressure. Cyclization to the title compounds was highly diastereoselective, producing each hexahydropyrrolo[1,2-a]-quinoline as a single stereoisomer with the all-*cis* geometry. The competing processes have not been observed in previous heterocyclization studies but can be attributed to greater strain in the system, which slows the final ring closure.

Introduction.

We previously reported an efficient tandem reduction-double reductive amination route to 2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylic esters [2]. Closure of this angular 6-6-6 tricyclic system was found to be highly diastereoselective for the production of the all-*cis* isomer. Furthermore, the reaction was relatively clean, giving only two minor products from side reactions in closing the second ring. In the current project, we had an interest in extending the scope of this transformation to the preparation of the corresponding 1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-5-carboxylic esters. Of particular interest was the comparative yield and selectivity of the reaction for the synthesis of the more highly strained 6-6-5 ring system [3].

The target heterocycle is relatively rare in nature. One notable example, however, is the alkaloid gephyrotoxin (**2**), a non-competitive blocker of neuromuscular transmission. While **2** incorporates the fully reduced 6-6-5 cyclic framework, one reported synthesis (Equation 1) proceeds
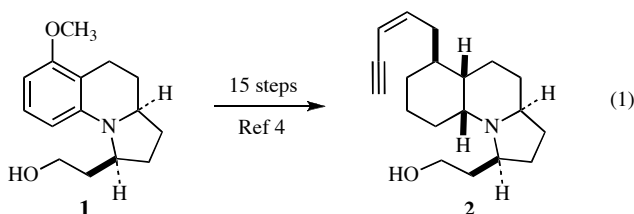
through a hexahydropyrrolo[1,2-a]quinoline intermediate, *e.g.* **1** [4,5]. Since gephyrotoxin and other neurotoxins have pharmacological value in the study of ion channel blockers, it is important to have synthetic access to these compounds.

Two previous syntheses of hexahydropyrrolo[1,2-a]-quinolines have been reported as part of efforts to prepare gephyrotoxin [4,5]. These were based on a Diels-Alder cyclization of an *o*-quinone methide *N*-substituted imine [4] and an intramolecular Schmidt reaction of an azide with a benzo-fused cyclopentyl carbocation [5]. Two additional syntheses of the unsubstituted ring system have involved metallation and alkylation of an *N*-formamidoyl-activated tetrahydroquinoline in the presence of pentynyl copper [6] and transition metal-promoted intramolecular coupling of an amine with an aryl halide [7]. All of these methods required elaborate synthetic schemes to prepare the cyclization substrates or special catalysts to effect ring closure. Additionally, the unsubstituted cases provided little information on selectivity in the ring closure or tolerance to other functionality. We report here a simple, efficient and diastereoselective tandem reduction-double reductive amination approach to the synthesis of substituted 1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolines using readily available precursors.

Results and Discussion.

The synthesis of the cyclization substrates is summarized in Scheme 1. Bromodiene **4a** was prepared by alkylating the dianion of methallyl alcohol with allyl

(1)

bromide and converting the resulting alcohol to the bromide with phosphorus tribromide [8]; bromodiene **4b** was prepared by the same method but used methallyl bromide as the alkylating agent. Alkylation of the anion of methyl (2-nitrophenyl)acetate (**3**) with **4a** and **4b** [9] gave the nitro dienoic esters **5a** and **5b**, respectively. Ozonolysis of these dienes followed by reductive workup then yielded a mixture of the dicarbonyl products and their methanol acetals [2]. Treatment of each mixture with 3% aqueous perchloric acid in tetrahydrofuran (1:1 v/v) [10] gave the required nitro dicarbonyl substrates.
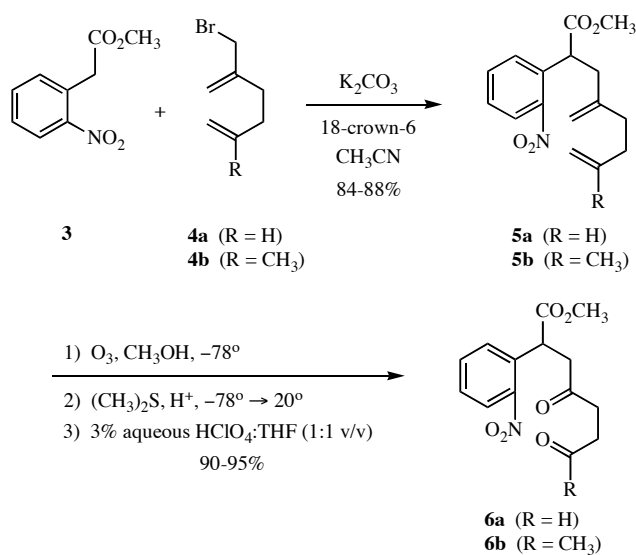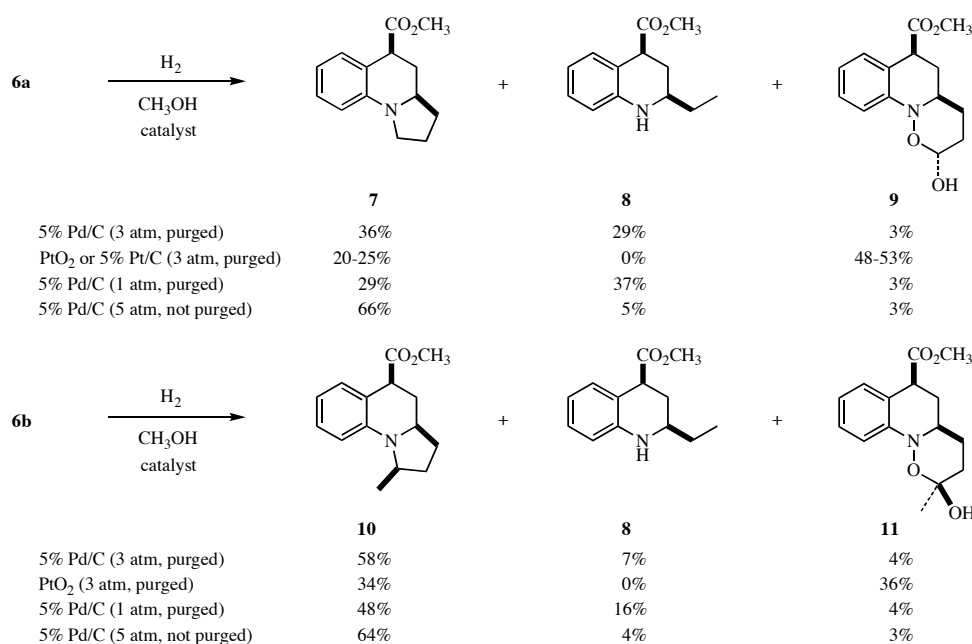
The results of our reductive cyclization studies are shown in Scheme 2 [11]. All reactions were done in a stainless steel reactor using a Paar shaker. In our initial experiment with **6a**, the reactor was evacuated and flushed with hydrogen three times prior to starting the shaker. After 3 hours under 3 atmospheres of hydrogen, a modest 36% yield of the hexahydropyrrolo[1,2-*a*]-quinoline **7** was isolated, along with 29% of tetrahydroquinoline **8** resulting from single ring closure and aldehyde decarbonylation [12] and 3% of a fused cyclic hemiacetal product **9** derived from capture of the intermediate hydroxylamine by the side chain carbonyls. Substrate **6b** followed a similar path giving **10**, **8** and **11**, although the deacylation required to produce tetrahydro-quinoline **8** was much less efficient.

Since palladium-on-carbon has often been observed to decarbonylate aldehydes [13,14], we sought to minimize this pathway by using platinum-based catalysts. With platinum oxide (and also 5% platinum-on-carbon for **6a**), the decarbonylation and deacylation processes were completely suppressed, but yields of the desired tricyclic products were lower and much larger proportions of the hemiacetals were observed. This suggests that platinum catalysts are less effective in reducing aromatic nitro groups [15], especially in the final stage of the reaction where the N-O bond of the hydroxylamine must be cleaved. This slower reduction allows for trapping of the intermediate hydroxylamine by the side chain carbonyls.

The disappointing results with platinum catalysts led us to further investigate the use of 5% palladium-on-carbon. Our first experiment evaluated the use of lower

Scheme 1

The results of Scheme 1 reaction.

Scheme 2

6a		7	8	9
5% Pd/C (3 atm, purged)		36%	29%	3%
PtO$_2$ or 5% Pt/C (3 atm, purged)		20-25%	0%	48-53%
5% Pd/C (1 atm, purged)		29%	37%	3%
5% Pd/C (5 atm, not purged)		66%	5%	3%

| 6b		10	8	11
5% Pd/C (3 atm, purged)		58%	7%	4%
PtO$_2$ (3 atm, purged)		34%	0%	36%
5% Pd/C (1 atm, purged)		48%	16%	4%
5% Pd/C (5 atm, not purged)		64%	4%	3%

hydrogen pressure for the reaction of **6a**. Under 1 atmosphere of hydrogen, the yield of tricyclic **7** decreased to 29% while the yield of decarbonylation product **8** increased to 37%; the proportion of hemiacetal **9** remained nearly constant at 3%. Substrate **6b** gave similar results. Thus, reduced pressures seem to favor the decarbonylation process.

Based upon this finding, we realized that purging the reactor prior to initiating the reaction (as was done in the initial experiments) exposed the substrates to low pressures of hydrogen in the presence of the catalyst and perhaps reduced the yield of **7** and **10**. The procedure was, therefore, modified to minimize exposure of the substrate to these conditions. After placing **6a**, solvent and catalyst in the reactor, the system was evacuated once, shaking was started and the hydrogen pressure was rapidly increased to 5 atmospheres. Assay of the products from this run showed a much higher 66% yield of **7** with only 5% of **8** and 3% of **9**. A similar improvement was also noted in the cyclization of **6b**. Thus, the desired tricyclic product appears to be favored at more elevated hydrogen pressures with 5% palladium-on-carbon.

The mechanism of the ring closure to form the 6-6-5 tricyclic system is the same as that previously proposed for the formation of the 6-6-6 structure (see Scheme 3). Reduction of the aromatic nitro compound to aniline **12** is followed by double reductive amination, first with the closest carbonyl to yield **14** and then with the more distant carbonyl to produce the hexahydropyrrolo[1,2-*a*]quinoline derivative **7** or **10**. The all-*cis* geometry of the product is dictated by the carboxylic ester group in **13** and **15**, which blocks one face of the molecule forcing hydrogen to add from the opposite side of the structure for both reductive

aminations. The shape of the molecule following the first reductive amination also contributes to the selectivity in the reduction of **15**.

The process leading to decarbonylation of aldehyde **6a** has substantial precedent in the literature [13,14] (see Scheme 4). Following initial cyclization to tetrahydroquinoline **14a** [12], oxidative addition of the side chain aldehyde to palladium on the surface of the catalyst would form the acyl palladium complex **16**. Migratory de-insertion of carbon monoxide would then give the alkyl palladium complex **17** and reductive elimination would release the decarbonylated tetrahydroquinoline **8**. Normally, aldehyde decarbonylation requires heating at 150-200° [13,14], but in the presence of a high concentration of hydrogen on the catalyst surface, the process can apparently proceed at much lower temperature.

Scheme 4

THQ = 2-(1,2,3,4-tetrahydroquinolyl)
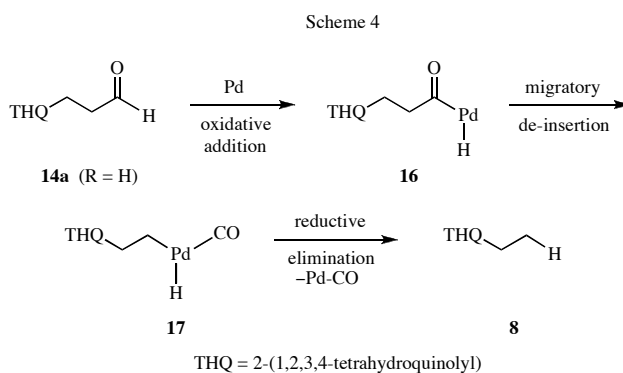
There is much less precedent for the deacylation of ketone **6b**. A possible mechanism, however, would involve initial 1,2-insertion of **14b** into a Pd-H bond to generate oxygen-bound intermediate **18**, followed by β-methyl elimination to give aldehyde **14a** and decarbonylation as described above (see Scheme 5).

Scheme 5

THQ = 2-(1,2,3,4-tetrahydroquinolyl)
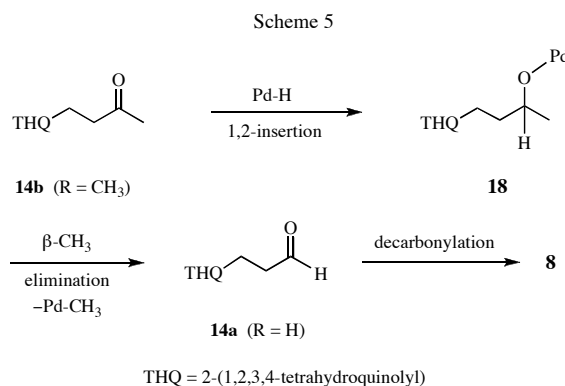
Scheme 3

Finally, the hemiacetal product results from partial reduction of **6** to **19** and capture of the hydroxylamine by the side chain carbonyls (see Scheme 6). Cyclization of the
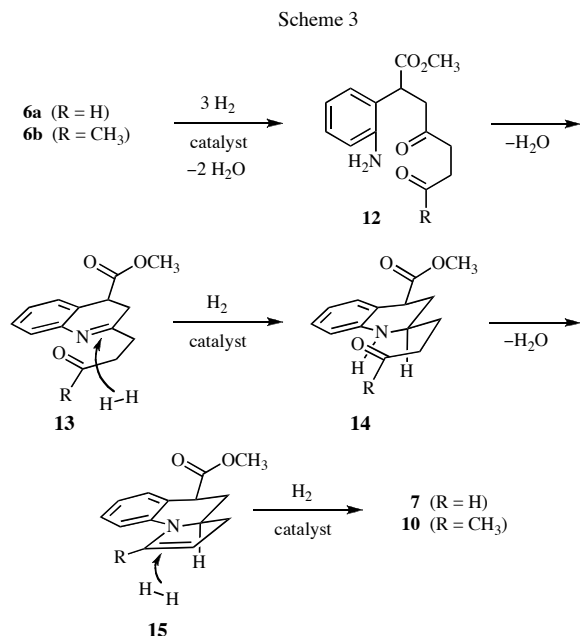
hydroxylamine on the proximal carbonyl and loss of water would give enamine **20** [2]. Reduction of the enamine from the side opposite the ester would then generate the ring closed *N*-hydroxytetrahydroquinoline **21** having the side chain *cis* to the ester. Finally, attack of *N*-hydroxy group on the second side chain carbonyl would produce the hemiacetal. The origin of selectivity in the hemiacetal closure is unclear. The equatorial OH in **9** was confirmed by a single crystal X-ray structure [16] and suggests that a steric preference rather than an anomeric effect [17] guides the ring closure. The axial OH in **11** was deduced from the NOESY spectrum [18], which showed no interaction of the C-1 methyl with any other protons in the molecule; this is only possible if the methyl occupies an equatorial position. The observed stereochemistry in **11** would also be expected on steric grounds [19,20], but such an argument would not predict this to be the exclusive product.

Scheme 6
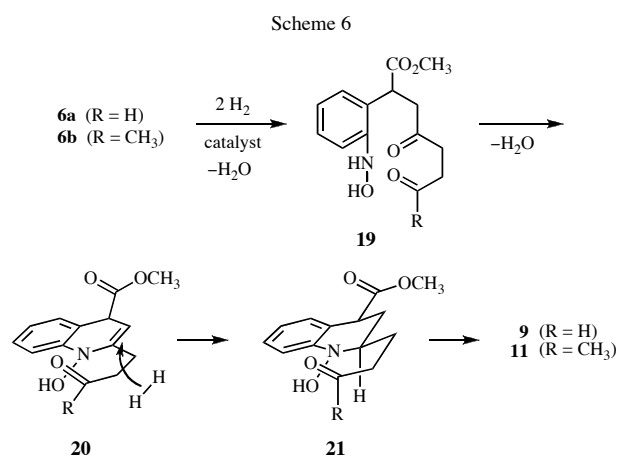
Conclusions.

Our earlier tandem reduction-double reductive amination used to prepare hexahydro-1*H*-benzo[*c*]-quinolizines has been successfully adapted for the preparation of the more strained hexahydropyrrolo[1,2-*a*]-quinoline framework. The reaction was found to exhibit the same high diastereoselectivity for the all-*cis* product, but added strain in the smaller ring system slowed the cyclization sufficiently to permit significant side reactions. These competing processes were largely circumvented by careful adjustment of catalyst and hydrogen pressure and useful yields of the desired tricyclic products were obtained. Further work is underway to identify other reductive cyclizations that can be optimized by tuning the reaction conditions.

EXPERIMENTAL

All reactions (except hydrogenations) were run under dry nitrogen in oven-dried glassware. Potassium carbonate was ground to a fine powder, dried under vacuum at 120° for 24 hours and stored in an oven at 120°. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [21] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^{1}H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (J) are given in Hertz. Mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

2-(Bromomethyl)-1,5-hexadiene (**4a**).

This compound (9.57 g, 41%) was prepared in two steps from 20 g (0.278 moles) of methallyl alcohol using the method described by Trost and Shi [8]. The physical and spectral properties matched those reported [8].

2-(Bromomethyl)-5-methyl-1,5-hexadiene (**4b**).

Methallyl alcohol was converted to its dianion on a 0.278-mole scale as described by Trost and Shi [8] and alkylated with 28.1 g (0.208 moles) of methallyl bromide to give 17.0 g (65%) of 2-methylene-5-methyl-5-hexen-1-ol, bp 70-72° at 3 mm Hg; ir: 3386, 3072, 1647, 906 cm^{-1}; ^{1}H nmr: δ 5.04 (m, 1H), 4.90 (m, 1H), 4.73 (m, 1H), 4.70 (m, 1H), 4.09 (s, 2H), 2.20 (m, 2H), 1.74 (d, 3H, J = 1.1), 1.61 (br s, 1H); ^{13}C nmr: δ 148.7, 145.4, 110.1, 109.5, 65.9, 35.9, 31.2, 22.4; ms: *m/z* 126 (M$^+$).

Anal. Calcd. for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.06; H, 11.20.

Reaction of this alcohol with 18.3 g (6.36 mL, 0.068 moles) of phosphorus tribromide in ether at 0° containing 1.0 g of pyridine as outlined for **4a** [8] gave 13.8 g (54%) of **4b** as a light yellow oil, bp 52° at 4 mm Hg; ir: 3078, 1643, 906, 889 cm^{-1}; ^{1}H nmr: δ 5.18 (m, 1H), 4.98 (m, 1H), 4.75 (m, 1H), 4.72 (m, 1H), 3.99 (s, 2H), 2.38 (t, 2H, J = 7.6), 2.19 (t, 2H, J = 7.6), 1.75 (s, 3H); ^{13}C nmr: δ 145.1, 144.9, 115.1, 110.4, 36.8, 35.5, 31.3, 22.4; ms: *m/z* 188/190 (M$^+$/M$^+$+2, *ca*.1:1).

Anal. Calcd. for $C_8H_{13}Br$: C, 50.79; H, 6.88. Found: C, 51.08; H, 6.96.

Representative Procedure for Alkylation of Methyl (2-Nitro-phenyl)acetate: Methyl (±)-4-Methylene-2-(2-nitrophenyl)oct-7-enoate (**5a**).

The general procedure of Makosza and Tyrala was used [9]. To a stirred solution of 0.98 g (5.00 mmoles) of **3** in 25 mL of dry acetonitrile was added 10 mg of 18-crown-6 and 5.8 g (42.0 mmoles) of anhydrous potassium carbonate. To the resulting blue mixture was added a solution of 1.05 g (6.00 mmoles) of **4a** in 5 mL of dry acetonitrile. The reaction was stirred at 60° for 8 hours, then cooled to room temperature. The solids were removed by filtration and the filtrate was concentrated under vacuum. The remaining oil was purified by flash column chromatography on a 25 cm x 2 cm silica gel column eluted with increasing concentrations of ether in hexanes to give 1.27 g

(88%) of **5a** as a light yellow oil. ir: 1738, 1643, 1528, 1351, 998, 909 cm^{-1}; ^{1}H nmr: δ 7.87 (d, 1H, J = 8.2), 7.58 (m, 2H), 7.42 (m, 1H), 5.79 (ddt, 1H, J = 16.9, 10.4, 6.0), 5.02 (dm, 1H, J = 16.9), 4.96 (dm, 1H, J = 10.4), 4.78 (d, 1H, J = 0.8), 4.71 (d, 1H, J = 0.8), 4.47 (dd, 1H, J = 8.2, 7.1), 3.66 (s, 3H), 2.88 (dd, 1H, J = 15.0, 8.5), 2.54 (dd, 1 H, J = 14.7, 7.1), 2.14 (m, 4H); ^{13}C nmr: δ 172.8, 149.6, 145.1, 138.0, 133.0, 132.9, 129.9, 128.1, 124.7, 114.8, 112.2, 52.3, 44.5, 39.2, 35.1, 31.8; ms: *m/z* 289 (M$^+$).

Anal. Calcd. for C$_{16}$H$_{19}$NO$_4$: C, 66.44; H, 6.57; N, 4.84. Found: C, 66.61; H, 6.64; N, 4.66.

Methyl (±)-7-Methyl-4-methylene-2-(2-nitrophenyl)oct-7-enoate (**5b**).

This compound (1.25 g, 84%) was isolated as a light yellow oil. ir: 1738, 1528, 1351, 892 cm^{-1}; ^{1}H nmr: δ 7.87 (dm, 1H, J = 7.9), 7.57 (m, 2H), 7.42 (m, 1H), 4.78 (s, 1H), 4.71 (m, 2H), 4.68 (m, 1H), 4.48 (dd, 1H, J = 7.9, 6.8), 3.67 (s, 3H), 2.89 (ddd, 1H, J = 14.7, 8.2, 0.8), 2.56 (ddd, 1H, J = 14.7, 7.1, 0.8), 2.14 (s, 4H), 1.72 (s, 3H); ^{13}C nmr: δ 172.8, 149.8, 145.5, 145.3, 133.0, 132.9, 129.9, 128.1, 124.7, 112.0, 110.1, 52.3, 44.5, 39.2, 35.9, 34.0, 22.4; ms: *m/z* 303 (M$^+$).

Anal. Calcd. for C$_{17}$H$_{21}$NO$_4$: C, 67.33; H. 6.93; N, 4.62. Found: C, 67.14; H, 6.99; N, 4.55.

Representative Procedure for Ozonolysis of the Dienes: Methyl (±)-2-(2-Nitrophenyl)-4,7-dioxoheptanoate (**6a**).

A solution of 1.00 g (3.46 mmoles) of **5a** in 125 mL of methanol was treated with ozone at −78° until thin layer chromatography indicated complete consumption of starting material. Excess ozone was removed on a stream of dry nitrogen and 4.99 g (5.90 mL, 80.5 mmoles) of dimethyl sulfide and 100 mg of *p*-toluenesulfonic acid were added. The mixture was gradually warmed to room temperature and stirred for 6 hours. The reaction was concentrated, diluted with ether, washed with saturated sodium bicarbonate (two times) and saturated sodium chloride (one time) and dried (magnesium sulfate). Removal of the ether gave the keto acetal containing a small amount of the keto aldehyde.

This mixture was dissolved in 40 mL of tetrahydrofuran and 40 mL of 3% aqueous perchloric acid was added dropwise at 0° [10]. The solution was stirred at 0° for 1 hour and at room temperature for 4 hours then extracted with dichloromethane (two times). The organic layer was washed with saturated sodium bicarbonate (two times) and saturated sodium chloride (one time), dried (magnesium sulfate) and concentrated under vacuum to give 0.91 g (90%) of **6a** as a light yellow oil. This compound was used without further purification. ir: 2840, 2725, 1737, 1715, 1528, 1351 cm^{-1}; ^{1}H nmr: δ 9.78 (s, 1H), 7.98 (dd, 1H, J = 8.1, 1.6), 7.59 (td, 1H, J = 7.6, 1.4), 7.45 (td, 1H, J = 7.6, 1.6), 7.44 (d, 1H, J = 8.1), 4.72 (dd, 1H, J = 8.5, 4.9), 3.65 (s, 3H), 3.52 (dd, 1H, J = 17.7, 8.5), 2.92 (dd, 1H, J = 18.0, 4.9), 2.79 (m, 4H); ^{13}C nmr: δ 205.5, 200.2, 172.1, 150.1, 133.5, 133.2, 131.0, 128.5, 125.2, 52.5, 45.2, 42.9, 37.4, 34.6; ms: *m/z* 293 (M$^+$).

Methyl (±)-2-(2-Nitrophenyl)-4,7-dioxooctanoate (**6b**).

This compound (0.96 g, 95%) was isolated as a light yellow oil. ir: 1739, 1715, 1528, 1351 cm^{-1}; ^{1}H nmr: δ 7.97 (dd, 1H, J = 8.1, 1.4), 7.58 (td, 1H, J = 7.5, 1.6), 7.45 (td, 1H, J = 7.5, 1.4), 7.43 (d, 1H, J = 8.1), 4.71 (dd, 1H, J = 8.5, 4.9), 3.65 (s, 3H), 3.51 (dd, 1H, J = 17.7, 8.5), 2.92 (dd, 1H, J = 18.0, 4.9), 2.72

(m, 4H), 2.17 (s, 3H); ^{13}C nmr: δ 206.8, 206.0, 172.1, 148.6, 133.4, 133.2, 130.9, 128.4, 125.2, 52.4, 45.2, 42.7, 36.8, 35.9, 29.7; ms: *m/z* 307 (M$^+$).

Reductive Cyclization of **6a**.

Caution: Though we never experienced any problems, addition of 5% palladium-on-carbon to methanol can cause fires. This operation should be performed under a nitrogen atmosphere.

A solution of 500 mg (1.71 mmoles) of **6a** in 125 mL of methanol containing 100 mg of 5% palladium-on-carbon was placed in a stainless steel pressure vessel in a Paar apparatus. The vessel was evacuated once, shaking was initiated and the apparatus was rapidly pressurized to *circa* 5 atmospheres (75 psi) with hydrogen gas. The reaction was continued for 3 hours at 30°. At the end of this time, hydrogen was purged from the reactor and the crude reaction mixture was concentrated. The residue was diluted with ether, and filtered through a pad of Celite topped with a layer of anhydrous magnesium sulfate to remove the catalyst. Removal of the ether gave a yellow oil that was purified by preparative thin layer chromatography to give three major bands. Band 1 contained methyl (±)-(3a*R**,5*S**)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-5-carboxylate (**7**); band 2 gave methyl (±)-(2*R**,4*S**)-2-ethyl-1,2,3,4-tetra-hydroquinoline (**8**); band 3 yielded the cyclic hemiacetal **9** derived from methyl (±)-(2*R**,4*S**)-1-hydroxy-2-(3-oxopropyl)-1,2,3,4- tetrahydroquinoline- 4-carboxylate.

Methyl (±)-(3a*R**,5*S**)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]-quinoline-5-carboxylate (**7**).

This compound (260 mg, 66%) was isolated as a white solid, mp 73-75°; ir: 1736 cm^{-1}; ^{1}H nmr: δ 7.10 (tm, 1H, J = 8.2), 6.93 (d, 1H, J = 7.5), 6.57 (td, 1H, J = 7.5, 1.1), 6.42 (dd, 1H, J = 8.2, 1.1), 3.93 (dd, 1H, J = 12.3, 5.2), 3.77 (s, 3H), 3.41 (dddd, 1H, J = 14.9, 10.4, 5.2, 3.0), 3.26 (m, 2H), 2.34 (ddd, 1H, J = 12.3, 5.2, 3.0), 2.10 (m, 2H), 1.91 (m, 1H), 1.82 (dt, 1H, J = 12.3, 11.5), 1.54 (m, 1H); ^{13}C nmr: δ 175.1, 144.4, 128.3, 127.0, 118.0, 115.2, 110.8, 56.3, 51.9, 46.9, 44.6, 32.9, 31.5, 23.6; ms: *m/z* 231 (M$^+$).

Anal. Calcd. for C$_{14}$H$_{17}$NO$_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.88; H, 7.41; N, 5.93.

Methyl (±)-(2*R**,4*S**)-2-Ethyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (**8**).

This compound (19 mg, 5%) was isolated as a white solid, mp 84-85°; ir: 3386, 1732 cm^{-1}; ^{1}H nmr: δ 7.02 (tm, 1H, J = 7.6), 6.96 (dm, 1H, J = 7.9), 6.63 (td, 1H, J = 7.6, 1.4), 6.50 (dd, 1H, J = 7.9, 1.1), 3.94 (dd, 1H, J = 12.0, 5.7), 3.79 (br s, 1H), 3.76 (s, 3H), 3.19 (dtd, 1H, 11.2, 6.3, 2.7), 2.20 (ddd, 1H, J = 12.8, 5.7, 2.7), 1.93 (ddd, 1H, J = 12.8, 12.0, 11.2), 1.56 (dq, 2H, J = 13.9, 7.5), 1.00 (t, 3H, J = 7.5); ^{13}C nmr: δ 175.0, 144.6, 128.1, 127.9, 118.1, 117.5, 114.7, 52.1, 52.0, 43.8, 32.0, 29.2, 9.8; ms: *m/z* 219 (M$^+$).

Anal. Calcd. for C$_{13}$H$_{17}$NO$_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.40; H, 7.83; N, 6.26.

Methyl (±)-(2*R**,4*S**)-1-Hydroxy-2-(3-oxopropyl)-1,2,3,4-tetra-hydroquinoline-4-carboxylate Cyclic Hemiacetal **9**.

This compound (14 mg, 3%) was isolated as a light yellow oil that crystallized on standing. Recrystallization from petroleum ether gave a light yellow solid, mp 124-126°; X-ray details [16];

ir: 3420, 1735 cm^{-1}; ^{1}H nmr: δ 7.32 (dd, 1H, J = 8.4, 1.4), 7.18 (tm, 1H, J = 8.2), 7.03 (dt, 1H, J = 7.9, 1.1), 6.88 (td, 1H, J = 7.6, 1.4), 5.16 (ddd, 1H, J = 9.3, 6.8, 2.2), 3.99 (t, 1H, J = 8.8), 3.75 (s, 3H), 3.63 (br s, 1H), 3.05 (m, 1H), 2.21 (d, 1H, J = 8.8), 2.18 (m, 1H), 2.02 (dm, 1H, J = 12.0), 1.88 (dm, 1H, J = 10.6), 1.71-1.45 (complex, 2H); ^{13}C nmr: δ 174.3, 146.0, 128.0, 127.7, 121.8, 121.0, 117.1, 97.3, 56.4, 52.2, 43.1, 31.9, 31.8, 30.0; ms: *m/z* 263 (M$^+$).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.92; H, 6.49; N, 5.26.

Reductive Cyclization of **6b**.

This reaction was run on 500 mg (1.63 mmoles) of **6b** as described for **6a**. Purification by preparative thin layer chromatography gave three major bands. Band 1 contained methyl (±)-(1*R**, 3a*R**, 5*S**)- 1- methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-5-carboxylate (**10**); band 2 gave methyl (±)-(2*R**,4*S**)-2-ethyl-1,2,3,4-tetrahydroquinoline (**8**); band 3 yielded the cyclic hemiacetal **11** derived from methyl (±)-(2*R**,4*S**)-1-hydroxy- 2- (3- oxobutyl)-1, 2, 3, 4-tetrahydroquinoline-4-carboxylate.

Methyl (±)-(1*R**,3a*R**,5*S**)-1-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-5-carboxylate (**10**).

This compound (256 mg, 64%) was isolated as a light tan oil that darkened on standing. Prolonged storage at 0° gave tan crystals, mp 62-64°; ir: 1736 cm^{-1}; ^{1}H nmr: δ 7.08 (tm, 1H, J = 8.2), 6.99 (dm, 1H, J = 7.6), 6.55 (td, 1H, J = 7.6, 1.1), 6.49 (d, 1H, J = 8.2), 3.98 (dd, 1H, J = 12.3, 6.0), 3.84 (quintet, 1H, J = 6.6), 3.75 (s, 3H), 3.40 (m, 1H), 2.36 (ddd, 1H, J = 12.3, 6.0, 2.2), 2.02 (m, 2H), 1.87 (dt, 1H, J = 12.3, 11.5), 1.70 (m, 2H), 1.17 (d, 3H, J = 6.3); ^{13}C nmr: δ 175.4, 143.7, 128.0 (2), 118.4, 115.1, 111.5, 57.5, 52.3, 52.0, 44.8, 33.0, 31.7, 30.3, 19.9; ms: *m/z* 245 (M$^+$).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.47; H, 7.76; N, 5.71. Found: C, 73.58; H, 7.81; N, 5.61.

Methyl (±)-(2*R**,4*S**)-2-Ethyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (**8**).

This compound (15 mg, 4%) was isolated as a white solid. The physical and spectral properties matched those given above.

Methyl (±)-(2*R**,4*S**)-1-Hydroxy-2-(3-oxobutyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate Cyclic Hemiacetal **11**.

This compound (14 mg, 3%) was isolated as a light yellow oil that darkened on standing. ir: 3467, 1735 cm^{-1}; ^{1}H nmr: δ 7.31 (dd, 1H, J = 8.2, 1.4), 7.20 (tm, 1H, J = 8.2), 7.04 (dt, 1H, J = 7.6, 1.1), 6.90 (td, 1H, J = 7.6, 1.4), 4.24 (br s, 1H), 4.03 (dd, 1H, J = 11.2, 6.8), 3.76 (s, 3H), 3.14 (m, 1H), 2.32-2.15 (complex, 2H), 1.89-1.75 (complex, 4H), 1.50 (s, 3H); ^{13}C NMR: δ 174.1, 145.7, 128.1, 127.5, 122.2, 121.8, 117.6, 98.3, 56.5, 52.2, 43.1, 34.5, 32.4, 27.0, 26.0; ms: *m/z* 277 (M$^+$).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.86; N, 5.05. Found: C, 65.09; H, 6.94; N, 4.93.

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[15]   Poisoning of the catalyst surface by the tetrahydroquinoline products may play a role in deactivating the platinum catalysts, see ref 8, pp 16-17, 318 and 385.
[16]   X-ray details for compound **9**: Intensity data were measured on a Bruker APEXII diffractometer with MoKα radiation (λ = 0.71073 Å) at 298(2) K. The structure was solved and refined using the Bruker SHELXTL (Version 6.1) software package. Formula: $C_{14}H_{17}NO_4$, crystal size: 0.30 x 0.20 x 0.06 mm, formula weight: 263.29, a = 8.2069(2) Å, b = 12.2899(3) Å, c = 13.5240(4) Å, β = 103.026(2)°, V = 1328.96(6) Å^3, Z = 4, monoclinic space group P2$_1$/n, density (calculated) = 1.316 Mg/m^3, 1489 independent reflections, 1170 observed reflections (I > 2.0(σI)), R$_1$ = 0.0335 (observed data), wR$_2$ = 0.0957 (all data). CCDC 290046 contains the supplementary crystallographic data for **9**. These data can be obtained free of charge from the CCDC at www.ccdc.cam.ac.uk/data_request/cif.
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