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Exploratory studies towards a total synthesis of the unusual bridged tetracyclic *Lycopodium* alkaloid lycopladine H

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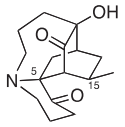
ABSTRACT

A strategy for a total synthesis of the structurally novel *Lycopodium* alkaloid lycopladine H has been investigated. Key steps that have been tested include: 1. a regioselective Diels–Alder cycloaddition of nitroethylene with an *o*-quinone ketal to produce the bicyclo[2.2.2]octane moiety of the alkaloid; 2. a stereoselective Henry reaction to generate the requisite functionality and configuration at C-5; 3. a stereoselective catalytic hydrogenation of a trisubstituted alkene to set the C-15 methyl configuration.

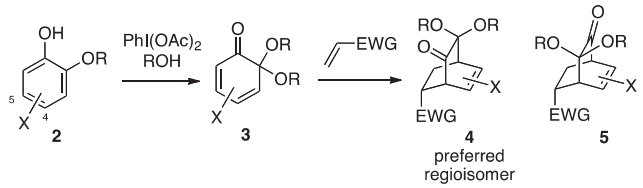
1. Introduction and background[1]

Lycopladine H (**1**) is a new member of the *Lycopodium* family of alkaloids that was recently isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*.[1,2] The structure of **1**, which was established by spectral analysis, incorporates some novel features including a 3-piperidone spiro-fused to a bicyclo [2.2.2]octane ring system. This structure is quite different from all other known *Lycopodium* alkaloids and therefore presents a unique synthetic challenge.[2] We have recently begun to explore a strategy directed towards a total synthesis of lycopladine H (**1**) based upon a Diels–Alder reaction of an *o*-quinone ketal to construct the bicyclo[2.2.2]octane moiety of the alkaloid, and some of these initial studies are the subject of this report.



1 lycopladine H

o-Quinone ketals like **3** and related cyclohexadienones are easily prepared from 2-substituted phenols **2** by oxidation, often using hypervalent iodine compounds in alcoholic solvent, although other methods are also available (Scheme 1).[3] Dienones **3** have been used as the 4π component in both inter- and intra-molecular Diels–Alder cycloadditions with a variety of electron rich and electron deficient dienophiles. With the latter type of dienophile, such as acrylates and α,β-unsaturated ketones, the regioisomeric adduct that is usually observed is **4** rather than **5**.[4] In addition, the electron withdrawing group is in an *endo* position in the cycloadduct. Interestingly, it has not been possible to rationalize the regiochemistry of this type of cycloaddition by computation.[5] However, one major drawback of using *o*-quinone ketals as dienes is the tendency of some to undergo rapid Diels–Alder dimerization. Therefore, these species are commonly generated and trapped in situ in the presence of an appropriate dienophile.



Scheme 1.

2. Results and discussion

Our initial plan was to effect an intramolecular [4+2]-cycloaddition of a cyclohexadienone using a dehydroamino acid derivative as the dienophile to establish the C-5 functionality and bicyclo[2.2.2]octane framework of the alkaloid. Although such dienophiles have not been utilized with *o*-quinone ketals and related systems, they have been applied successfully in other

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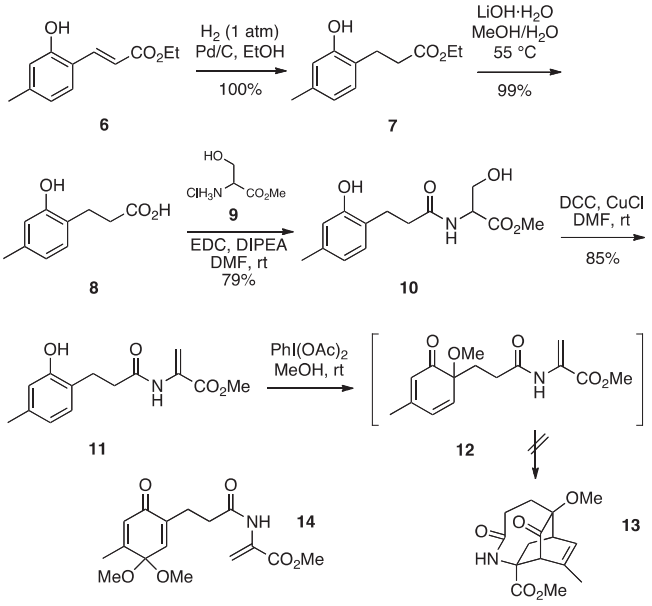
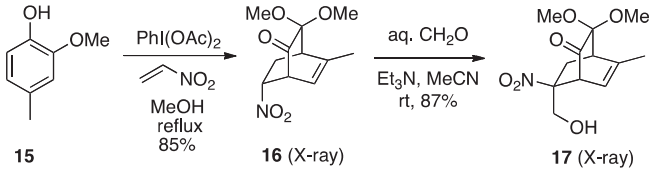
Diels–Alder reactions.[6] Therefore, known α,β-unsaturated ester **6**[7] was hydrogenated to produce **7** in high yield (Scheme 2). Hydrolysis of ester **7** gave acid **8**, which was condensed with serine methyl ester hydrochloride (**9**) to yield amide **10**. It was then possible to cleanly dehydrate alcohol **10** using DCC and a catalytic amount of cuprous chloride[8] to afford the requisite Diels–Alder precursor **11**. Phenol **11** was next treated with diacetoxyiodobenzene (DAIB) in methanol at rt in order to generate the cyclohexadienone intermediate **12**, but under these conditions none of the desired Diels–Alder adduct **13** was detected. Rather, only the *p*-quinone mono ketal **14** could be isolated in 40% yield. Similarly, attempted oxidation of **11** with DIAB under other sets of conditions or with lead tetraacetate did not afford a [4+2]-cycloadduct but only led to a complex mixture of decomposition products containing some cyclohexadienone dimers.



Scheme 2.

In view of the disappointing results described above, at this juncture we turned to an alternative approach involving an intermolecular Diels–Alder reaction. We decided to first test the chemistry with methoxyphenol **15** since it is an inexpensive commercially available compound, even though we anticipated that Diels–Alder reactions of the derived *o*-quinone ketal with electron deficient dienophiles would lead to the undesired *C*-methyl regioisomer. Our plan here was to employ nitroethylene as the dienophile. This compound is known to be highly reactive in [4+2]-cycloadditions,[9] although to our knowledge it has not previously been used with cyclohexadienones.

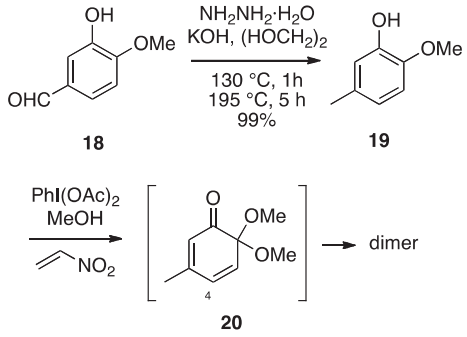
We were pleased to find that oxidation of phenol **15** with DIAB in methanol in the presence of nitroethylene (3 equiv) afforded Diels–Alder adduct **16** as a single regio- and stereo-isomer in high yield (Scheme 3). The composition of this adduct was established by X-ray crystallography. Although the *C*-methyl substituent in **16** is in the incorrect position for the alkaloid, it was decided to test the further elaboration of this intermediate. Thus, a Henry reaction of



Scheme 3.

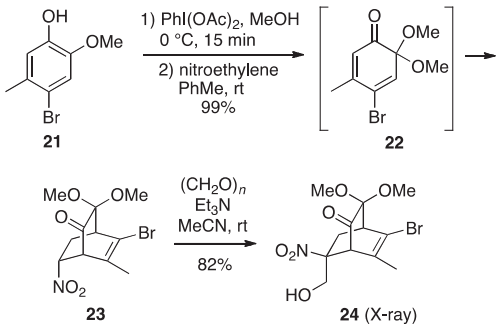
nitro compound **16** using aqueous formaldehyde and triethylamine as the base led to stereoselective formation of the desired *endo* hydroxymethyl compound **17** in 87% isolated yield.[10] The structure of this product was again confirmed by X-ray analysis.

Based on these promising results, the correct phenolic precursor for lycopladine H (**1**) was investigated. Since the requisite methoxyphenol **19** is commercially available but rather expensive, we have conveniently prepared this material on a ~25 g scale by a Wolff–Kishner reduction of isovanillin (**18**) (Scheme 4).[11] Treatment of phenol **19** with DIAB in the presence of nitroethylene as was done for the regioisomer **15**, however, did not give any of the desired Diels–Alder adduct but led only to dimerization of the cyclohexadienone **20**. This result is not too surprising since it is well documented that *o*-quinone ketals, which are unsubstituted at C-4 tend to be prone to dimerization.[4b–d] A good solution to this problem is to use the strategy developed by Liao and co-workers, which involves installing a replaceable blocking group at this position of the starting phenol.[4b–d]



Scheme 4.

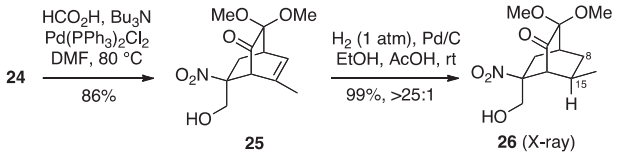
Therefore, the known *p*-bromophenol **21**, prepared as previously described via NBS halogenation of compound **19**,[4d] was used as the precursor for the Diels–Alder step (Scheme 5). Brief exposure of this compound to DIAB in methanol at 0 °C, followed by stirring with nitroethylene (1.5 equiv) in toluene at rt led to the desired Diels–Alder adduct **23** in high yield. It might be noted that the 4-bromo-*o*-quinone ketal intermediate **22** is stable and can even be chromatographed on silica gel. Using conditions previously developed for the Henry reaction of **16** (cf. Scheme 3), nitro compound **23** was then cleanly transformed to the *endo* hydroxymethyl product **24**. X-ray analysis of this compound established its structure and stereochemistry to be as shown.



Scheme 5.

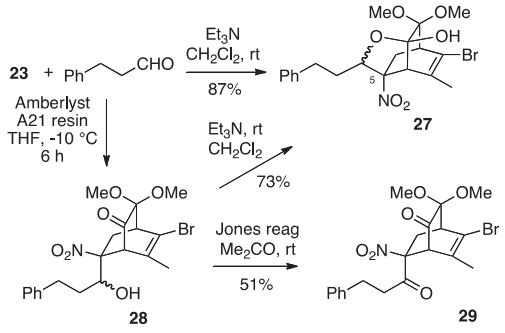
The unwanted bromine substituent in **24** could be easily removed via the Pd-promoted procedure described by the Liao group to give alkene **25** in good yield (Scheme 6).[4d] The next operation to be investigated was the reduction of the olefin double bond of **25** to set the correct C-15 stereochemistry of the alkaloid. Our initial assumption was that in order to control the stereochemistry of this

reduction, a metal-directed hydrogenation would have to be employed, which makes use of the *endo* hydroxymethyl group in **25**. Therefore, hydrogenations were attempted using [Ir(cod)(py)(PCy_3)]PF_6 or [Rh(nbd)(dppb)]BF_4 as catalysts at hydrogen pressures up to 500 psi, but in no case was any reduction product **26** observed, with only starting material being recovered. We were surprised to find, however, that simply hydrogenating the C-8,15 alkene double bond (lycopladine H numbering) of compound **25** with 10% Pd/C at 1 atm afforded the desired C-15 *exo*-methyl product **26** with >25:1 stereoselectivity in nearly quantitative yield. The stereostructure of **26** was subsequently proven by X-ray crystallography. Interestingly, under these hydrogenation conditions, the nitro group was untouched. This hydrogenation stereoselectivity is undoubtedly of steric origin, although one might not have predicted this result a priori.



Scheme 6.

In order to develop a synthetic approach to lycopladine H (**1**), which is potentially more convergent than that described above, we have examined the possibility of utilizing a more complex aldehyde than formaldehyde in the Henry reaction. In these studies, hydrocinnamaldehyde was used as a model. Interestingly, we have observed that the outcome of these condensations depends upon the specific reaction conditions used. For example, to our surprise condensation of nitro compound **23** with hydrocinnamaldehyde under experimental conditions similar to those used for the Henry reaction with formaldehyde led to the undesired *exo* alkylation product **27** (78%), which exists as the cyclic hemiketal (inseparable ~3:2 epimer mixture) (Scheme 7). We speculated that perhaps the Henry reaction with hydrocinnamaldehyde is reversible, and that under these conditions the kinetic *endo* product **28** is labile, leading to formation of the presumably more stable *exo* hemiketal product **27**.[10] It was therefore decided to explore other conditions for the Henry reaction. We were pleased to find that condensation of nitro compound **23** with hydrocinnamaldehyde in the presence of dry Amberlyst A21 ion exchange resin in THF at −10 °C led to the desired *endo* adduct **28** as an inseparable mixture of alcohol epimers. Alcohol **28**, however, was found to be rather unstable towards chromatographic purification on silica gel (see Experimental section). Therefore, the crude material was directly oxidized with Jones reagent in acetone to afford stable diketone **29** in 51% overall yield for the two steps.



Scheme 7.

In order to test our postulate that the Henry reaction is reversible, a purified sample of the *endo* condensation product **28** was exposed to the reaction conditions used for the direct formation of the *exo* adduct **27** from nitro compound **23** (i.e., triethylamine, methylene chloride, rt). This experiment indeed led to the formation of hemiketal **27** (~3:2 epimer mixture) in 73% yield. Interestingly, it was possible to detect the formation of small amounts of hydrocinnamaldehyde by TLC during the course of this reaction. Moreover, simply allowing a sample of alcohol **28** stand at rt led to slow conversion to ketal **27**.

3. Conclusion

We have tested the feasibility of executing a strategy for synthesis of lycopladine H (**1**). Pivotal operations include an intermolecular regioselective Diels–Alder reaction of 4-bromo-*o*-quinone ketal (**22**) with nitroethylene to construct the bicyclo[2.2.2]octane core **23** of the alkaloid. In addition, it is possible to effect stereoselective Henry (nitro aldol) reactions of this adduct to set the correct stereochemistry for C-5 of the alkaloid. Finally, the stereochemistry at the methyl-bearing C-15 of **1** can be established by a stereoselective catalytic hydrogenation of the C-8,15 alkene of intermediate **25**. We are currently utilizing what we have learned in the course of the work outlined here to complete a total synthesis of lycopladine H.[12]

4. Experimental

4.1. General methods

All non-aqueous reactions were carried out under a positive atmosphere of argon in flame-dried glassware unless otherwise noted. Anhydrous THF, CH_2Cl_2 and DMF were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, or DRX-400 MHz spectrometers. Infrared spectral data were recorded using a Perkin–Elmer 1600 FTIR. Flash column chromatography was performed using Sorbent Technologies silica gel 60 (230–400 mesh).

4.2. Synthesis and characterization

*4.2.1. (E)-Ethyl 3-(2-hydroxy-4-methylphenyl)acrylate (**6**).* To a solution of 2-hydroxy-4-methylbenzaldehyde (6.75 g, 49.58 mmol) in CH_2Cl_2 (150 mL) was added (carbethoxymethylene)triphenylphosphorane (19.0 g, 54.54 mmol). The solution was stirred for 2 h at rt and the solvent was evaporated. The crude material was purified by flash column chromatography (1:2 EtOAc/hexanes) to give cinnamate ester **6** (10.13 g, 99%) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J=16.1 Hz, 1H), 7.41 (br s, 1H), 7.34 (d, J=8.2 Hz, 1H), 6.71 (m, 2H), 6.63 (d, J=16.1 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 2.29 (s, 3H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 155.9, 142.5, 141.3, 129.3, 121.6, 119.1, 117.2, 117.0, 60.8, 21.5, 14.4; HRMS (ES-TOF) $[M-H]^-$ calcd for $C_{12}H_{13}O_3$ 205.0865, found 205.0872.

*4.2.2. Ethyl 3-(2-hydroxy-4-methylphenyl)propanoate (**7**).* To a solution of cinnamate ester **6** (1.70 g, 8.24 mmol) in EtOH (40 mL) was added 10% palladium on carbon (170 mg). The suspension was placed under hydrogen gas (1 atm) and stirred overnight. The reaction mixture was filtered through a pad of Celite, which was washed with EtOAc. The filtrate was evaporated to yield propanoate ester **7** (1.71 g, 100%) as a clear oil of sufficient purity for use in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (br s, 1H), 6.98 (d, J=7.5 Hz, 1H), 6.71 (s, 1H), 6.69 (d, J=7.6 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 2.88 (t, J=6.5 Hz, 2H), 2.69 (t, J=6.6 Hz, 2H), 2.27 (s, 3H), 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 154.2, 138.0, 130.4, 124.3, 121.6, 117.7, 61.3, 35.4, 24.5, 21.0, 14.2; HRMS (ES-TOF) $[M-H]^-$ calcd for $C_{12}H_{15}O_3$ 207.1021, found 207.1015.

*4.2.3. 3-(2-Hydroxy-4-methylphenyl)propanoic acid (**8**).* To a solution of propanoate ester **7** (1.00 g, 4.80 mmol) in MeOH (18 mL) and

water (6 mL) was added lithium hydroxide hydrate (1.00 g, 23.83 mmol). The suspension was heated at 55 °C and stirred overnight. The resulting orange solution was cooled and poured into 1 M HCl (30 mL) and ice (30 g). The aqueous mixture was extracted with EtOAc. The organic extract was dried over $MgSO_4$ and evaporated to give acid **8** (856 mg, 99%) as an off-white solid of sufficient purity for use in the next step: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (br s, 1H), 9.20 (br s, 1H), 6.93 (d, J=7.5 Hz, 1H), 6.60 (s, 1H), 6.51 (d, J=7.5 Hz, 1H), 2.71 (t, J=7.7 Hz, 2H), 2.45 (t, J=7.7 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.3, 155.0, 136.3, 129.5, 123.9, 119.6, 115.6, 33.9, 25.2, 20.8; HRMS (ES-TOF) $[M-H]^-$ calcd for $C_{10}H_{11}O_3$ 179.0708, found 179.0706.

*4.2.4. Methyl 3-hydroxy-2-(3-(2-hydroxy-4-methylphenyl)propanamido)propanoate (**10**).* To a solution of acid **8** (750 mg, 4.16 mmol) in DMF (20 mL) were added D,L-serine methyl ester hydrochloride (**9**, 710 mg, 4.56 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (880 mg, 4.59 mmol) and diisopropylethylamine (2.50 mL, 14.35 mmol). The resulting solution was stirred overnight at rt and the reaction mixture was concentrated to ~5 mL. To the crude mixture was added 0.1 M HCl (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with (0.1 M) HCl, water and brine, dried over $MgSO_4$ and evaporated to give amide **10** (929 mg, 79%) as a white solid in sufficient purity for use in the next step: mp 132–133 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.15 (d, J=7.5 Hz, 1H), 6.91 (d, J=7.5 Hz, 1H), 6.58 (s, 1H), 6.50 (d, J=7.5 Hz, 1H), 5.02 (t, J=5.3 Hz, 1H), 4.34 (q, J=6.5 Hz, 1H), 3.68–3.58 (m, 2H), 3.62 (s, 3H), 2.67 (t, J=7.7 Hz, 2H), 2.38 (t, J=7.7 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 171.3, 154.9, 136.0, 129.4, 124.3, 119.6, 115.6, 61.3, 54.7, 51.8, 35.1, 25.3, 20.8; HRMS (ES-TOF) $[M+H]^+$ calcd for $C_{14}H_{20}NO_5$ 282.1341, found 282.1332.

*4.2.5. Methyl 2-(3-(2-hydroxy-4-methylphenyl)propanamido)acrylate (**11**).* To a solution of alcohol **10** (250 mg, 0.889 mmol) in DMF (8 mL) were added CuCl (22 mg, 0.222 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (190 mg, 0.921 mmol). The reaction mixture was stirred for 20 h at rt and the solvent was evaporated. EtOAc (40 mL), water (20 mL) and saturated NH_4Cl (20 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated. The residue was purified via filtration through a silica gel plug with Et_2O to give acrylate **11** (200 mg, 85%) as an off-white solid: mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.81 (br s, 1H), 6.95 (d, J=7.5, 1H), 6.72 (s, 1H), 6.66 (d, J=7.6 Hz, 1H), 6.60 (d, J=0.8 Hz, 1H), 5.90 (d, J=0.8 Hz, 1H), 3.82 (s, 3H), 2.91 (t, J=6.2 Hz, 2H), 2.74 (t, J=6.1 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 164.5, 154.5, 138.2, 130.4, 127.8, 124.4, 121.5, 118.2, 110.0, 53.2, 38.4, 24.1, 21.2; HRMS (ES-TOF) $[M+H]^+$ calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1235.

*4.2.6. Methyl 2-(3-(3,3-dimethoxy-4-methyl-6-oxocyclohexa-1,4-dien-1-yl)propanamido)acrylate (**14**).* To a solution of phenolic acrylate **11** (120 mg, 0.456 mmol) in MeOH (9 mL) was added (diacetoxy)iodobenzene (160 mL, 0.498 mmol). The reaction mixture was stirred for 20 h at rt and the solvent was evaporated. The residue was purified by flash column chromatography (40% EtOAc in hexanes) to give *p*-quinone ketal **14** (53 mg, 40%) as a white solid: ^{1}H NMR (300 MHz, CD_3CN) δ 7.95 (br s, 1H), 6.51 (s, 1H), 6.31 (s, 1H), 6.07 (d, J=1.3 Hz, 1H), 5.66 (d, J=1.3 Hz, 1H), 3.70 (s, 3H), 3.05 (s, 6H), 2.53–2.43 (m, 4H), 1.77 (s, 3H).

*4.2.7. endo-3,3-Dimethoxy-5-methyl-7-nitrobicyclo[2.2.2]oct-5-en-2-one (**16**).* To a solution of (diacetoxy)iodobenzene (15.7 g, 48.7 mmol) and nitroethylene (9.0 mL, 132 mmol) in methanol (175 mL) was added 2-methoxy-4-methylphenol (**15**, 5.6 mL, 44.3 mmol). The mixture was heated at reflux and stirred for 20 h, cooled to rt, and the solvent was evaporated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to yield cycloadduct **16** (9.08 g, 85%) as a light yellow solid. X-ray quality crystals were obtained via slow evaporation from CH_2Cl_2/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, J=6.0 Hz, 1H), 4.85 (m, 1H), 3.76 (dd, J=6.0, 2.5 Hz, 1H), 3.29 (s, 3H), 3.24 (s, 3H), 2.97 (d, J=2.6 Hz, 1H), 2.52 (m, 1H), 2.12 (dt, J=14.3, 3.9 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 146.6, 116.0, 93.6, 79.8, 52.1, 50.6, 49.8, 42.7, 26.4, 21.0; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{11}H_{18}BrN_2O_5$ 337.0399, found 337.0411.

*4.2.8. 7-(Hydroxymethyl)-3,3-dimethoxy-5-methyl-7-nitrobicyclo[2.2.2]oct-5-en-2-one (**17**).* To a solution of nitro compound **16** (100 mg, 0.414 mmol) in acetonitrile (2 mL) were added aqueous formaldehyde (35%, 100 μL, 1.26 mmol) and triethylamine (60 μL, 0.430 mmol). The resulting solution was stirred for 2 days and the solvent was evaporated. The residue was purified by flash column chromatography (40% EtOAc in hexanes) to give nitro alcohol **17** (97 mg, 87%) as a white solid. X-ray quality crystals were obtained via slow evaporation from CH_2Cl_2/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, J=6.9, 0.9 Hz, 1H), 4.06, 3.61 (ABq, J=11.0 Hz, 2H), 3.92 (d, J=7.0 Hz, 1H), 3.37 (s, 3H), 3.23 (s, 3H), 3.01 (q, J=2.6 Hz, 1H), 2.73 (dd, J=14.8, 3.0 Hz), 1.95 (d, J=1.6 Hz, 3H), 1.64 (dd, J=14.8, 2.8 Hz, 1H); HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{12}H_{20}BrN_2O_6$ 367.0505, found 367.0498.

*4.2.9. 2-Methoxy-5-methylphenol (**19**).* To isovanillin (**18**, 10.0 g, 65.7 mmol) in ethylene glycol (130 mL) were added KOH (37 g, 659 mmol) and hydrazine hydrate (16 mL, 330 mmol). The reaction mixture was heated at 130 °C for 1 h, then at 190 °C for 5 h. The solution was cooled to rt, then poured into a mixture of concd HCl (85 mL) and ice (300 g). The acidic aqueous layer was extracted with Et_2O. The organic extract was dried over $MgSO_4$ and evaporated to give phenol **19** (8.97 g, 99%) as a low-melting white solid in sufficient purity for use in the next step. Spectral data were consistent with literature values.[4d]

*4.2.10. endo-5-Bromo-3,3-dimethoxy-6-methyl-7-nitrobicyclo[2.2.2]oct-5-en-2-one (**23**).* To (diacetoxyiodo)benzene (24.50 g, 76.06 mmol) in MeOH (275 mL) at 0 °C was added bromophenol **21**[2] (15.00 g, 69.10 mmol). The reaction mixture was stirred for 15 min, and water (250 mL) and brine (250 mL) were added. The aqueous mixture was extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to give *o*-quinone ketal **22**. To the crude material was added a solution of nitroethylene in PhMe (1 M, 120 mL, 120 mmol), and the resulting solution was stirred overnight at rt. The solvent and residual nitroethylene were removed under reduced pressure. The crude material was purified by flash column chromatography (20% EtOAc in hexanes) to give cycloadduct **23** (21.95 g, 99%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (m, 1H), 3.85 (d, J=2.4 Hz, 1H), 3.37 (s, 3H), 3.35 (t, J=3.0 Hz, 1H), 3.29 (s, 3H), 2.71 (ddd, J=14.3, 9.8, 2.8 Hz, 1H), 2.33 (ddd, J=14.4, 4.6, 3.4 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 131.4, 119.6, 93.8, 79.3, 59.0, 50.8, 50.6, 48.3, 28.7, 20.0; IR (thin film) 1747, 1556 cm^{-1}; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{11}H_{18}BrN_2O_5$ 337.0399, found 337.0406.

*4.2.11. 5-Bromo-7-(hydroxymethyl)-3,3-dimethoxy-6-methyl-7-nitrobicyclo[2.2.2]oct-5-en-2-one (**24**).* To a solution of nitro compound **23** (550 mg, 1.72 mmol) in MeCN (8 mL) were added aqueous formaldehyde (35%, 410 μL, 5.15 mmol) and triethylamine (240 μL, 1.72 mmol). The bright yellow reaction mixture was stirred for 24 h at rt, and the solvent was evaporated. The residue was purified by flash column chromatography (2:1 hexanes/EtOAc) to yield nitro alcohol **24** (492 mg, 82%) as a white solid. X-ray quality crystals were obtained via slow evaporation from CH_2Cl_2/hexanes: mp 147 °C; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 4.14 (dd, J=12.1, 4.6 Hz, 1H), 3.97 (s, 1H), 3.45 (dd, J=12.1, 5.4 Hz, 1H), 3.35 (s, 3H), 3.31 (t, J=2.9 Hz, 1H), 2.69 (dd, J=14.8, 2.8 Hz, 1H), 2.58 (br t, J=5.3 Hz, 1H), 1.92 (s, 3H), 1.81 (dd, J=14.7, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 132.7, 120.8, 94.2, 93.3, 66.6, 58.3, 50.6, 49.9, 48.4, 32.6, 19.7; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{12}H_{20}BrN_2O_6$ 367.0505, found 367.0492.

*4.2.12. 7-(Hydroxymethyl)-3,3-dimethoxy-6-methyl-7-nitrobicyclo [2.2.2]oct-5-en-2-one (**25**).* To a solution of bromoalkene **24** (5.50 g, 15.71 mmol) in DMF (30 mL) were added formic acid (1.20 mL, 31.80 mmol), tributylamine (11.25 mL, 47.22 mmol) and bis(-triphenylphosphine)palladium(II) dichloride (220 mg, 0.313 mmol). The solution was heated at 80 °C and stirred for 18 h. The reaction mixture was cooled and filtered through a pad of Celite. The pad was washed with EtOAc (150 mL), and the filtrate was washed with water and brine. The organic phase was dried over $MgSO_4$ and evaporated. The resulting crude material was purified by flash column chromatography (1:1 hexanes/EtOAc) to give nitroalkene **25** (3.67 g, 86%) as a yellow solid: mp 141–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, J=6.5, 1.6 Hz, 1H), 4.10, 3.47 (ABq, J=12.2 Hz, 2H), 3.82 (d, J=1.2 Hz, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 3.08 (dt, J=6.5, 3.1 Hz, 1H), 2.67 (dd, J=14.6, 2.9 Hz, 1H), 2.43 (br t, J=7.7 Hz, 1H), 1.90 (d, J=1.6 Hz, 3H), 1.59 (dd, J=14.6, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 136.6, 128.9, 94.2, 93.8, 66.6, 56.9, 50.4, 49.2, 37.6, 32.8, 20.5; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{12}H_{21}N_2O_6$ 289.1400, found 289.1390.

*4.2.13. 6-(Hydroxymethyl)-3,3-dimethoxy-7-methyl-6-nitrobicyclo [2.2.2]octan-2-one (**26**).* To a solution of alkene **25** (1.00 g, 3.69 mmol) in EtOH (20 mL) was added 10% palladium on carbon (100 mg). The resulting suspension was placed under a hydrogen atmosphere (1 atm) and stirred for 24 h. The reaction mixture was filtered through a pad of Celite and the solids were washed with EtOAc. The organics were evaporated to give saturated nitro alcohol **26** (1.00 g, 99%) as an off-white solid as a single diastereomer (>25:1). X-ray quality crystals were obtained via slow evaporation from Et_2O: mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15, 3.88 (ABq, J=12.4 Hz, 2H), 3.22 (s, 3H), 3.08 (s, 3H), 2.97 (d, J=1.8 Hz, 1H), 2.76 (dt, J=15.4, 3.1 Hz, 1H), 2.41 (m, 1H), 1.76 (ddd, J=14.4, 10.7, 3.6 Hz, 1H), 1.64 (dd, J=15.4, 2.1 Hz, 1H), 1.26 (m, 1H), 0.99 (d, 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 98.1, 93.5, 65.8, 52.2, 49.7, 48.9, 33.6, 31.4, 28.3, 27.9, 20.8; HRMS (ES-TOF) $[M+H]^+$ calcd for $C_{12}H_{20}NO_6$ 274.1291, found 274.1282.

*4.2.14. 5-Bromo-7,7-dimethoxy-4-methyl-3-nitro-2-phenethyl-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-7a-ol (**27**).* (A) To a solution of nitro compound **23** (320 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) were added hydrocinnamaldehyde (90%, 160 μL, 1.09 mmol) and triethylamine (70 μL, 0.50 mmol). The dark yellow solution was stirred overnight, and then evaporated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to give hemiketal **27** (395 mg, 87%) as a white solid in a 3:2 mixture of diastereomers.

(B) To a solution of epimeric alcohols **28** (45 mg, 0.099 mmol) in CH_2Cl_2 (1 mL) was added triethylamine (14 μL, 0.100 mmol). The solution was stirred overnight at rt, and the solvent was evaporated. The residue was purified by preparative TLC (25% EtOAc in hexanes) to give hemiketal **27** (33 mg, 73%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 4.74 (s, 0.4H), 4.69 (s, 0.6H), 4.44 (dd, J=8.9, 3.2 Hz, 0.6H), 4.02 (dd, J=10.8, 2.9 Hz, 0.4H), 3.73 (s, 0.6H), 3.62 (s, 0.4H), 3.44 (s, 1.2H), 3.44 (s, 1.8H), 3.38 (s, 1.2H), 3.37 (s, 1.8H), 3.05 (m, 1H), 2.92 (m, 1H), 2.67 (m, 2H), 2.20 (dd, J=14.0, 2.6 Hz, 0.4H), 2.07 (dd, J=14.0, 2.5 Hz, 0.6H), 2.02 (m, 1H), 1.96 (s, 1.2H), 1.92 (s, 1.8H), 1.83 (m, 0.4H), 1.63 (m, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 140.8, 131.8, 131.7, 128.8, 128.7, 128.6, 128.5, 126.3, 126.2, 116.7, 116.4, 103.7, 103.6, 102.2, 101.4, 92.0, 91.1, 81.7, 80.1, 60.3, 55.9, 51.8, 51.7, 51.6, 48.0, 47.9, 40.3, 34.0, 32.6, 32.6, 31.2, 29.9, 20.4; IR (thin film) 3493, 1538 cm^{-1}; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{20}H_{28}BrN_2O_6$ 471.1131, found 471.1135.

*4.2.15. 5-Bromo-3,3-dimethoxy-6-methyl-7-nitro-7-(3-phenyl-propanoyl)bicyclo[2.2.2]oct-5-en-2-one (**29**).* To a solution of nitro compound **23** (640 mg, 2.00 mmol) in THF (10 mL) at −10 °C were added hydrocinnamaldehyde (400 μL, 3.04 mmol) and Amberlyst A21 ion exchange resin (400 mg). The resulting suspension was stirred and warmed to 0 °C over 6 h. The reaction mixture was filtered, and the resin was rinsed with EtOAc. The solvent was evaporated to give crude alcohol **28** as a 5:3 mixture of diastereomers. The alcohol was unstable to chromatography and was directly carried on to the next step. Alcohol **28** could be isolated by chromatography in low yield (~33%), but isomerizes to hemiketal **27** on standing overnight.

Crude alcohol **28** was dissolved in acetone (20 mL). Jones reagent (2.7 M in Cr, 1.10 mL, 2.97 mmol) was added dropwise over 10 min, and the resulting solution was stirred for 12 h at rt. The solution was quenched with *i*-PrOH (1 mL), and the reaction mixture was filtered through a silica gel plug, eluting with EtOAc. The combined organics were evaporated, and the residue was purified by flash column chromatography (20% EtOAc in hexanes) to give diketone **29** (457 mg, 51% over two steps) as a white solid: mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J=6.5 Hz, 2H), 7.21 (m, 3H), 3.85 (d, J=0.6 Hz, 1H), 3.44 (dd, J=18.5, 1.7 Hz, 1H), 3.38 (s, 3H), 3.20 (s, 3H), 2.93–2.84 (m, 5H), 2.69 (dd, J=14.9, 2.8 Hz, 1H), 1.60 (d, J=0.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 191.2, 139.6, 130.7, 128.8, 128.5, 126.8, 121.4, 97.8, 93.7, 59.7, 50.5, 50.1, 48.4, 37.9, 32.3, 29.7, 19.4; IR (neat) 1737, 1541 cm^{-1}; HRMS (ES-TOF) $[M+NH_4]^+$ calcd for $C_{20}H_{26}BrN_2O_6$ 469.0974, found 469.0978.

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