In a separate experiment when the reaction was carried out at 120 °C until the intermediate **1b** was no longer detectable (220 h), there was extensive decomposition and only the dimer **4b** was isolated in low (8%) yield.

3′,4′,5′,6′,7′,8′-Hexahydro-1,6′-dimethyl-5,5,8′,8′-tetraphenylspiro[piperidine-3,2-[2*H*]pyrano[3,2-*c*]pyridin]-4-ol (10). Method A. A solution–suspension of 1.3 g of **4a** and 0.6 g of KBH_4 in 75 mL of methanol was heated under reflux until the carbonyl function was no longer present as shown by IR spectroscopy (8 h). After the solvent was removed, the residue was taken up with cold water and the product extracted twice with 30 mL of $CHCl_3$. The combined $CHCl_3$ extracts were washed, dried (Na_2SO_4), and evaporated. Trituration of the residue with 2-propanol gave 0.96 g (73%) of **10**, mp 222–224 °C. An analytical sample of **10** was obtained by recrystallization from acetonitrile: mp 223–224 °C; IR ($CHCl_3$) 3560 (OH), 1690 (C=CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 10.0 Hz, 1 H, OH, D_2O exchangeable), 2.30 (s, 3 H, NCH_3), 2.45 (s, 3 H, NCH_3), 4.23 (d, J = 10.0 Hz, 1 H, CHO), 6.52–6.82 (m, 4 H, Ar), 6.92–7.40 (m, 16 H, Ar); mass spectrum, m/z 556. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 82.81; H, 7.27; N, 5.07.

Method B. To a stirred suspension of 2.0 g of $LiAlH_4$ in 50 mL of anhydrous tetrahydrofuran was added a solution of 5.5 g of **4a** in 25 mL of the same solvent and allowed to reflux until the carbonyl function was no longer detectable by IR spectroscopy (6 h). Ethyl acetate (150 mL) was added cautiously at 0 °C followed by the addition of water (100 mL). The organic phase was washed, dried (Na_2SO_4), and evaporated in vacuo to give 5.4 g of nearly colorless cake. Crystallization from acetonitrile gave 2.8 g of **10**, mp 223–224 °C. This product is identical with that obtained by method A. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 81.72; H, 7.36; N, 4.97.

Decahydro-2,8-dimethyl-4,4,6,6-tetraphenyl-4a,9a-epoxy-2*H*,7*H*-oxepino[3,2-*c*:6,7-*c*′]dipyridine (11). A solution of alcohol **10** (0.5 g) in 10 mL of 48% hydrobromic acid was heated on a steam bath for 1.5 h and the contents were subsequently poured onto ice water. The mixture was made basic with aqueous NH_3 and extracted twice with 25 mL of CH_2Cl_2. The CH_2Cl_2 extracts were washed, dried (Na_2SO_4), and evaporated to give 0.4 g of off-white solid. Trituration with 2-propanol gave 0.3 g of **11**, mp 248–249 °C dec. Recrystallization from acetonitrile gave analytically pure **11** as white crystals: mp 252–253 °C dec; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H, NCH_3), 2.28 (s, 3 H, NCH_3), 5.10 (d, J = 2 Hz, 1 H, C*H*O), 6.55–7.25 (m, 18 H, Ar), 7.71 (dd, J = 6.0 and 2.0 Hz, 2 H, Ar); mass spectrum, m/z 556. Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.98; H, 7.24; N, 5.03. Found: C, 81.70; H, 7.31; N, 5.06.

Acknowledgment. We express our thanks to U. Zeek for microanalyses and to Dr. R. C. Greenough, D. Housman, R. E. Saville, and R. B. Scott for the determination of spectra.

Registry No. **1a**, 96129-85-0; **1a** (4-oxime), 96129-89-4; **1a** (4-amine), 96129-90-7; **1a** (4-amine)·2HCl, 96129-91-8; **1a** (4-alcohol), 96129-92-9; **1a** (4-alcohol)·HCl, 96129-93-0; **1a** (4-2,2-diphenylacetate)·HCl, 96129-94-1; **1a** (3-oxime), 96129-95-2; **1a** (benzylidene derivative), 96129-96-3; **1a** (3,4-dimethoxybenzylidene derivative), 96129-97-4; **1b**, 96129-88-3; **2**, 781-35-1; **3**, 96129-86-1; **3**·2HCl, 96129-87-2; **4a**, 96129-98-5; **4b**, 96129-99-6; **10**, 96130-00-6; **11**, 96130-01-7; paraformaldehyde, 30525-89-4; $MeNH_2$·HCl, 593-51-1; $EtNH_2$·HCl, 557-66-4; $Ph_2CHCOCl$, 1871-76-7; PhCHO, 100-52-7.

Preparation of Optically Active, Functionalized *cis*-Δ^6-1-Octalones

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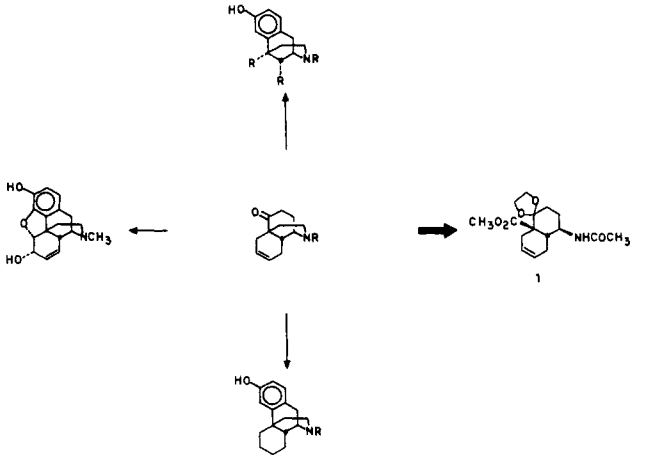
A preparation of optically pure, functionalized *cis*-Δ^6-1-octalones starting with (−)-β-pinene (92% ee) is detailed. The conversion of (−)-β-pinene to (−)-*cis*-nopinol (>97% ee) and its utilization in the preparation of (4*R*,9*R*,10*R*)-(+)-4-(acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone ethylene ketal (**1**), a *cis*-Δ^6-1-octalone possessing the correct absolute configuration at three appropriately functionalized chiral centers characteristic of the morphine-related analgesics, is described.

Central to the development of a divergent[2] synthesis of the morphine-related analgesics, including the morphinan- and benzomorphan-based analgesics, is the stereo- and enantiocontrolled synthesis of the aliphatic carbon framework composing the BC ring system of morphine. Control of the absolute configuration at three, contiguous stereocenters, C-9, C-13, and C-14 on the morphine skeleton, provides the necessary capabilities for a stereo- and enantioselective preparation of the morphine-based analgesics.[3,4] Herein we detail a preparation of (4*R*,9*R*,10*R*)-(+)-4-(acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone ethylene ketal (**1**), from (1*S*,5*S*)-(−)-β-pinene (**2**), which possesses the required absolute configuration at three functionalized chiral centers suitable for further elaboration to the morphine-related analgesics.



1

Optical Purification of Pinene Derivatives. (1*S*,5*S*)-(−)-β-Pinene (**2**) and its ozonolysis product

(1) (a) Searle Scholar recipient, 1981–1985. National Institutes of Health Career Development Award recipient, 1983–1988 (CA 00898). (b) National Institutes of Health predoctoral trainee, 1980–1983 (GM 07775).

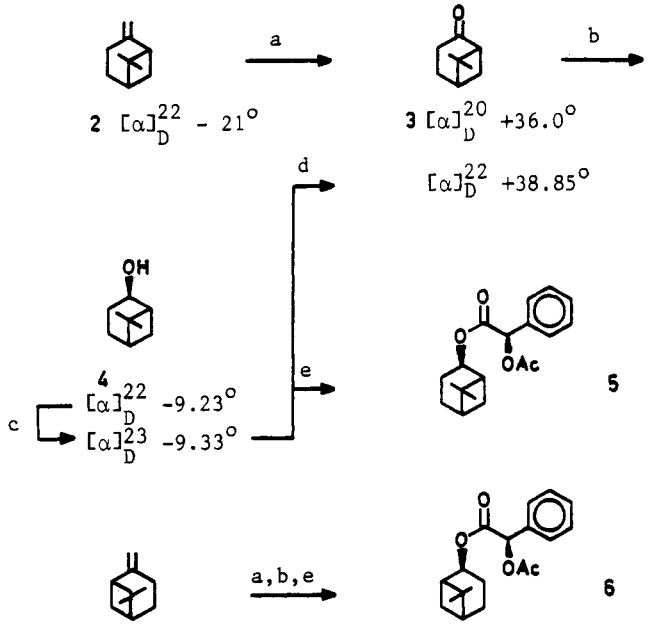
(2) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1984**, *49*, 4050.

(3) Lednicer, D., Ed. "Central Analgetics"; John Wiley & Sons, Inc.: New York, 1982. (b) Brossi, A. R. *Trends Pharmacol. Sci.* **1982**, *3*, 239. Schmidhammer, H.; Jacobson, A. E.; Brossi, A. *Med. Res. Rev.* **1983**, *3*, 1. (c) May, E. L. *J. Med. Chem.* **1980**, *23*, 225. Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. DeStevens, G. *Pure Appl. Chem.* **1969**, *19*, 89.

(4) For recent studies on the preparation of optically pure analgesics, see: Rice, K. C. *J. Org. Chem.* **1980**, *45*, 3135.

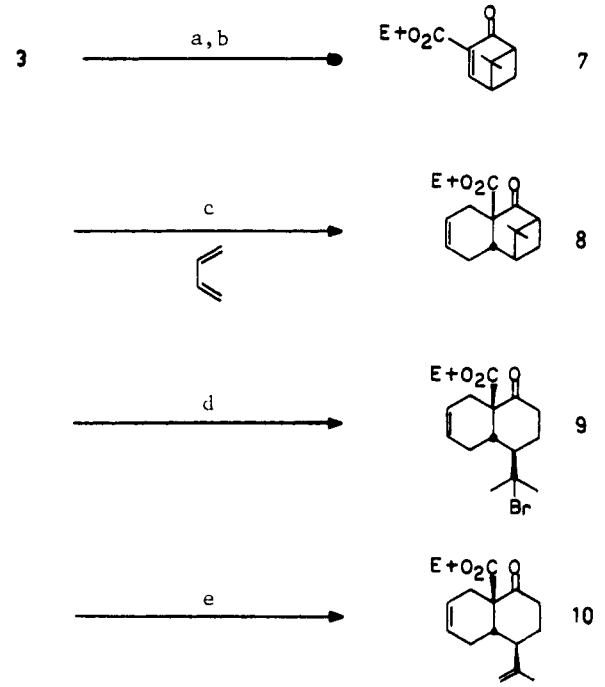
0022-3263/85/1950-1904$01.50/0

Scheme I[a]



[a] (a) O_3/O_2, CH_3OH; CH_3SCH_3. (b) $NaBH_4$, THF-H_2O, 75% for **4**. (c) Recrystallization (6x) from hexane, 53% recovery. (d) PDC, CH_2Cl_2, 95%. (e) (*R*)-(−)-*O*-Acetylmandelic acid, DCC, CH_2Cl_2, 93% for **5**.

Scheme II[a]



[a] (a) NaH, $(EtO)_2CO$, THF, 90%. (b) NaH, PhSeBr; H_2O_2, CH_2Cl_2-H_2O, 82%. (c) Xylene, 120 °C, 32 h, 82%. (d) BBr_3, CH_2Cl_2, 98%. (e) $(i\text{-Pr})_2NEt$, dioxane, **10** (62%) and **11** (30%).

(1*R*,5*S*)-(+)-nopinone (**3**) have served as inexpensive, chiral starting materials for chiral syntheses[5] and chiral reagents.[6] Despite their widespread applicability no useful procedure has been developed for the optical purification of commerically available, optically impure (−)-β-pinene[7] (ca. 92% ee) or (+)-nopinone.[8,9] The potential use of optically pure (1*R*,5*S*)-(+)-nopinone in the preparation of **1** provided the incentive for the examination of a simple, large scale method of achieving this optical purification, Scheme I.

Ozonolysis[8] of (1*S*,5*S*)-(−)-β-pinene (**2**) followed by sodium borohydride reduction[10a] afforded (1*R*,2*R*,5*S*)-*cis*-nopinol (**4**, $[\alpha]_D$ −9.23°, 1x recrystallized)[11] which was recrystallized repetitively. No significant enhancement of the optical rotation of **4** was observed after the third recrystallization.[13] The optical purity of (−)-*cis*-nopinol (recrystallized 6x) was assayed by formation of the (*R*)-*O*-acetylmandelate ester[14] **5**, Scheme I.[14b] The (*R*)-*O*-acetylmandelate ester of (1*S*,2*S*,5*R*)-(+)-nopinol (**6**), prepared from (1*R*,5*R*)-(+)-β-pinene,[15] was similarly prepared for comparison with **5**. The signals (singlets) for the *gem*-dimethyl groups of the diastereomeric esters are well separated in the proton NMR spectra (10.5–12.5 Hz). Only one diastereomer was detected in the proton NMR spectrum of **5** (limit of detection ≤2%). Oxidation of the recrystallized (1*R*,2*R*,5*S*)-(−)-*cis*-nopinol (**4**) with pyridinium dichromate (PDC)[16] afforded (1*R*,5*S*)-(+)-nopinone [**3**, $[\alpha]_D$ +38.85° (*c* 4.0, methanol)]. The highest reported optical rotations for **3** are $[\alpha]_D$ +39.0° (*c* 4, methanol) and $[\alpha]_D$ +39.9° (calcd).[8] Thus, the optical purity of **3** and **4** is in excess of 97%. A comparison of the optical rotations of **3** before (92% ee) and after (>97% ee) this procedure of optical purification suggests the material is in fact much purer (>99% ee).

Preparation of 1. The preparation of (4*R*,9*R*,10*R*)-(+)-4-(acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone ethylene ketal (**1**), from (1*R*,5*S*)-(+)-nopinone (**3**, >97% ee), is detailed in Schemes II and III.

(+)-Nopinone (**3**) was converted to enone **7**[17a] by sequential treatment with sodium hydride and diethyl carbonate, phenylselenenyl bromide,[17b] and hydrogen peroxide,[17b] Scheme II. Diels–Alder reaction of enone **7** with 1,3-butadiene (xylene, 120 °C, 32 h, 82% or catalytic Cu$(BF_4)_2$,[18] CH_2Cl_2, 25 °C, 12 h, 34%) afforded

(5) (a) Banthorpe, D. V.; Whittaker, D. *Chem. Rev.* **1966**, *66*, 643. (b) Hobbs, P. D.; Magnus, P. D. *J. Chem. Soc., Chem. Commun.* **1974**, 856. (c) Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1980**, *102*, 2737. Konopelski, J. P.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2297. (d) Moore, L.; Gooding, D.; Wolinsky, *J. Ibid.* **1983**, *48*, 3750. (e) Inokuchi, T.; Asanuma, G.; Torii, S. *Ibid.* **1982**, *47*, 4622 and references cited therein.

(6) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 393. Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Chem. Soc., Chem. Commun.* **1978**, 687.

(7) (a) (−)-β-Pinene is available from Aldrich Chemical Company. (b) For the optical purification of (−)-β-pinene, see: Comyns, A. E.; Lucas, H. J. *J. Am. Chem. Soc.* **1957**, *79*, 4339 and references cited therein.

(8) For an optical purification of (+)-nopinone, see: Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50.

(9) Optically pure α-pinene derived boranes have been prepared and utilized for the preparation of chiral compounds with essentially 100% ee, see: Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797; *J. Org. Chem.* **1984**, *49*, 945 and references cited therein.

(10) (a) Baretta, A. J.; Jefford, C. W.; Waegell, B. *Bull. Soc. Chim. Fr.* **1970**, 3985. (b) Jefford, C. W.; Burger, U. *Chimia* **1970**, *24*, 385.

(11) (1*R*,2*R*,5*S*)-(−)-*cis*-Nopinol (**4**) [(1*R*)-(1α,2β,5α)-6,6-dimethylbicyclo[3.1.1]heptan-2-ol] has been confusingly referred to as (−)-α-nopinol in early literature (see ref 5a) and more recently as 2β-hydroxyapopinane (see ref 12a); to avoid confusion we have adopted the usage of a more acceptable trival name for **4**, (−)-*cis*-nopinol, which unambiguously describes the stereochemical relationship of the *gem*-dimethyl-1,5-methano bridge and the hydroxyl group, (see ref 12b).

(12) (a) Hirata, T. *Bull. Chem. Soc.* **1972**, *45*, 3169. (b) Bessiere-Chretien, Y.; Grison, C. *Bull. Soc. Chim. Fr.* **1970**, 3103. Holden, C. M.; Whittaker, D. *Org. Magn. Reson.* **1975**, *7*, 125.

(13) Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates, and Resolution"; John Wiley and Sons: New York, 1981; p 423.

(14) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

(15) Harwood, L. M.; Julia, M. *Synthesis* **1980**, 456.

(16) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(17) (a) For the preparation of methyl 6,6-dimethyl-2-oxobicyclo-[3.1.1]heptane-3-carboxylate, see ref 5e. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(18) Copper(II) tetrafluoroborate was dried as described: Corey, E. J.; Koellicker, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, *93*, 1489 and a stock solution in dry methylene chloride (6.4 mg/mL) was prepared.

Table I. Studies on the Conversion of 8 to 10

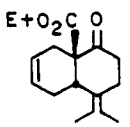
reagent (equiv)	cleavage of the cyclobutane ring of 8: conditions, time; temp, °C; solvent	result[a]
BBr_3 (1.2)	40 min; −93 to −100; CH_2Cl_2	**9** (98%)
(1.3)	15 min; −93 to −100; Et_2O	recovered **8**
(0.9)[b]	30 min; −78; CH_2Cl_2	**8** (30%), **10** (7%), i (31%),[c] ii (5%)[c]
(1.0)[b]	1.75 h; −78; CH_2Cl_2	**10** (22%), **11** (18%), i (35%)[c]
BCl_3 (1.0)	45 min; −78; CH_2Cl_2	recovered **8**
(1.0)[b]	2 h; 0; CH_2Cl_2	**8** (10%), **10** (10%), **11** (25%)
Me_3SiI (1.0)	2 h; −78; CH_2Cl_2	recovered **8**
	18 h; 25; CH_2Cl_2	ii only[c]
$AlCl_3$ (0.67)	2.5 h; 0; CH_2Cl_2	recovered **8**
Et_2AlCl (0.67)	2.5 h; 0; CH_2Cl_2	recovered **8**
p-TsOH (2.1)	20 h; 80; benzene	ii only[c]

base (equiv)	conversion of **9** to **10**/**11**: conditions, time; temp, °C; solvent	result[a]
(*i*-Pr)$_2$NEt (1.0)	66 h; 60–65; dioxane	**10** (62%), **11** (30%)
	3.25 h; 80; dioxane	**10** (46%), **11** (33%)
	19 h; 25; dioxane or toluene	recovered **9**
	6 h; 80; toluene	**10** (29%), **11** (24%)
t-BuOK[d] (1.3)	18 h; 25; toluene	recovered **9**
	12 h; 50; THF	**10** (28%), **11** (36%)
	19 h; 25; Me_2SO	**10** (44%), **11** (21%)
Et_3COK[e] (1.0)	7 h; 25; Me_2SO	**10** (58%), **11** (5%)[e]
DBU (1.1)	28 h; 25; toluene or dioxane	recovered **9**
	12 h; 50; dioxane	**10**:**11** (1:1)[f]
basic Al_2O_3	27 h; 0; hexane	**10**:**11** (<2:1)[f]

[a] All yields reported are for material purified by chromatography (SiO_2). [b] The reaction products were assayed after chromatography on SiO_2, which was demonstrated to promote the conversion of **9** to **10**/**11**. [c] See footnote 20a for structures i and ii. [d] 1.4 M *t*-BuOK (DME) was employed. [e] 1.5 M Et_3COK was prepared by the addition of potassium (1.0 equiv) to a solution of dry triethylcarbinol in toluene and the resulting mixture was warmed at 110 °C (8 h). The ratio of **10**:**11** ranged from 11.8–1:1 in variable yields. [f] Ratio of **10**:**11** determined by proton NMR.

(2*R*,4*S*,9*R*,10*S*)-(+)-3,3-dimethyl-9-(ethoxycarbonyl)-2,4-methano-*cis*-Δ^6-1-octalone (**8**). The *gem*-dimethyl-2,4-methano bridge in **7** serves to direct the Diels–Alder addition exclusively to the less hindered, α-face.

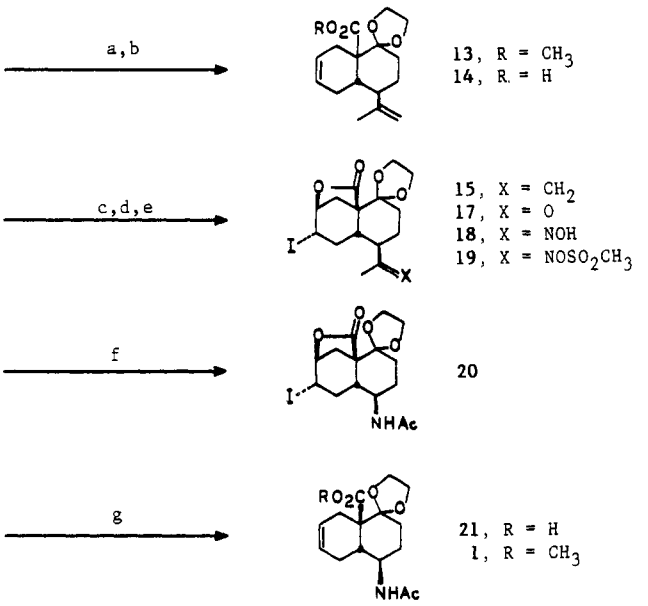
Central to the utilization of (−)-β-pinene in the preparation of optically active *cis*-Δ^6-1-octalones is the effective cleavage of the *gem*-dimethyl-2,4-methano bridge. A number of similar studies on the cleavage of the four-membered ring of substituted pinene and nopinone derivatives have been conducted with varying degrees of success. The cyclobutane ring of **8** was opened upon boron tribromide[19] treatment at −93 to −100 °C to afford the unstable bromide **9** in 98% yield. Treatment of **9** with diisopropylethylamine (dioxane, 60 °C, 65 h) afforded a mixture of the readily separable isopropenyl derivative **10** (62%) and isopropylidene derivative **11** (30%). The use



11

of the potassium salt of triethylcarbinol[5c] (dimethyl sulfoxide, 25 °C) for the conversion occasionally gave comparable yields of **10** with a better ratio of **10**:**11**. Alumina[5e] treatment of **9** gave **10** and **11** in a complex mixture of side products. Table I details representative results of a study on the optimization of the *yield* in the conversion of **8** to **10**. Although higher ratios of **10**:**11** could be achieved under a variety of conditions, the boron tribromide cleavage and diisopropylethylamine-promoted elimination, Scheme II, provided the highest isolated yield of **10** and proved to be dependably reproducible.

Scheme III[a]

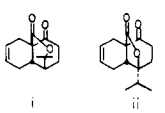


[a] (a) $HOCH_2CH_2OH$, *p*-TsOH catalyst, benzene, $-H_2O$, 91%. (b) EtSLi, HMPA, 91%. (c) I_2, KI, $NaHCO_3$, THF–H_2O, **15** (84%) and **16** (12%). (d) O_3/O_2, CH_3OH; CH_3SCH_3, 92%. (e) $NH_2OH\cdot HCl$, pyridine, DMAP; CH_3SO_2Cl, Et_3N, CH_2Cl_2. (f) SiO_2, $CHCl_3$, 25 °C, 54 h, 84% from **17**. (g) Zn, EtOH; CH_2N_2, ether, 90%.

Initial attempts to convert **10** to **12** by suitable differentiation of the two double bonds in **10** were only modestly successful, eq 1. Treatment of **10** with *m*-chloroperbenzoic acid (CH_2Cl_2, −78 to 0 °C, 6.5 h) gave a mixture of isopropenyl epoxide, cyclohexenyl epoxide, bis(epoxide), and a trace of Baeyer–Villiger product.[20] Treatment of **10** with *N*-bromosuccinimide (THF–H_2O, −18 to 25 °C) afforded the isopropenyl bromohydrin and bis(bromohydrin) (1:1) along with recovered starting material.[20b] Iodine–silver(II) oxide[21] treatment of **10** (dioxane–H_2O, 25 °C) gave a se-

(19) Levine, S. G.; Gopalakrishnan, B. *Tetrahedron Lett.* **1979**, 699. See also ref 5c.

(20) (a) Compound i was characterized: ^1H NMR ($CDCl_3$) δ 5.60 (m, 2 H, CH=CH), 3.20–1.15 (m, 10 H), 1.61 (s, 6 H, two CH_3's); IR ($CHCl_3$) ν_{max} 2930, 1740, 1710, 1275, 1120, 900 cm^{-1}; EIMS, *m*/*e* (relative intensity) 234 (M^+, 13), 219 (9), 216 (12), 189 (7), 180 (24), 161 (69), 133 (29), 126 (30), 120 (44), 105 (83), 91 (98), 84 (base), 81 (94), 77 (84), 69 (93). Compound ii is characterized: ^1H NMR ($CDCl_3$) δ 5.63 (m, 2 H, CH=CH), 3.05–1.20 (m, 10 H), 1.13 and 1.04 (two s, 3 H each, CH_3); IR (film) ν_{max} 2960, 1780, 1720, 1270, 1120, 985, 910 cm^{-1}; EIMS, *m*/*e* (relative intensity) 234 (M^+, 1), 190 (6), 175 (7), 127 (47), 120 (base), 107 (42), 99 (18), 91 (16), 77 (32), 55 (15).

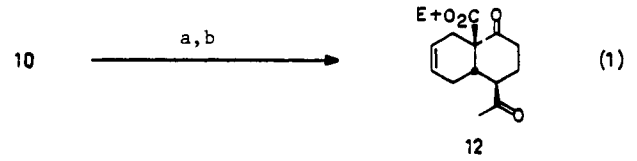


i ii

(b) The ^1H NMR spectrum of isopropenyl epoxide (bromohydrin) did not contain the isopropenyl proton signals (broad singlet). The spectrum of cyclohexene epoxide did not contain the cyclohexenyl proton signals (multiplet). The spectrum of bis(epoxide) (bisbromohydrin) product did not contain either set of olefinic proton signals. The spectrum of the postulated Baeyer–Villiger product contained both sets of olefinic signals and it was not identical with the starting material.

(21) Parrilli, M.; Barone, G.; Andinolfi, M.; Mangoni, L. *Tetrahedron Lett.* **1976**, 207.

parable mixture of isopropenyl epoxide and bis(epoxide) (5:3),[20b] and subsequent periodic acid cleavage of the isopropenyl epoxide (1.4 equiv of H_5IO_6, 1:1 dioxane–H_2O, 25 °C, 24 h) afforded **12**[22] in an unoptimized 25% overall yield from **10**.

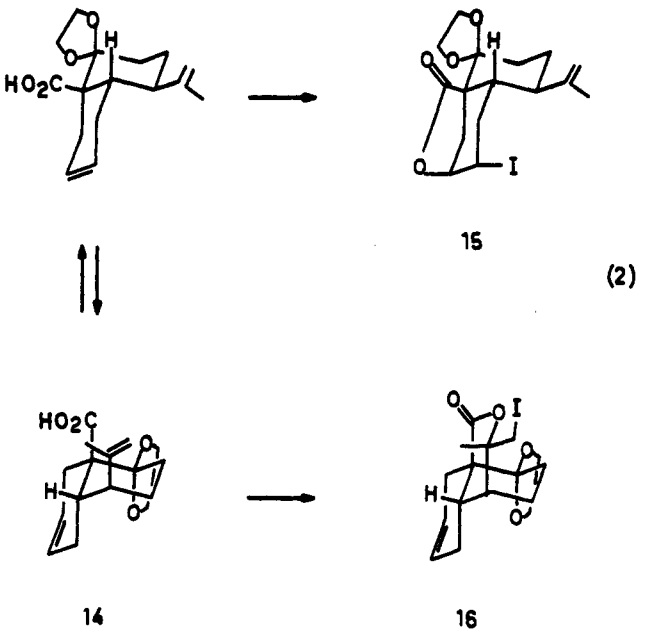


(1)

(a) I_2, AgO, dioxane, 55% isopropenyl epoxide.

(b) H_5IO_6, dioxane-H_2O (1:1), 45%.

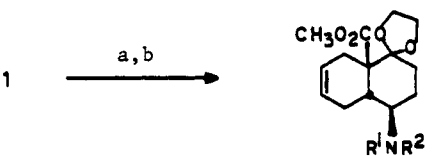
The two double bonds in **10** were successfully differentiated in the conversion of **10** to the iodo lactone **15**, Scheme III. Ethylene ketal **13** was prepared from **10** and treated with lithium ethanethiolate (hexamethylphosphoramide (HMPA), 100 °C, 2.5 h, 91%) to afford the carboxylic acid **14**.[23a] Attempts to deesterify **13** with excess lithium hydroxide (refluxing ethanol–water),[23b] the sodium salt of phenylselenol (THF–HMPA, 75–100 °C),[23c] anhydrous hydroxide (8.0 equiv of *t*-BuOK, 1.0 equiv of H_2O, THF, 25–75 °C),[23d] or lithium iodide–sodium cyanide (refluxing DMF)[23e] gave recovered starting material. Iodo lactonization[23b] of carboxylic acid **14** afforded the five-membered iodo lactone **15** (84%) and the six-membered iodo lactone **16** (12%).[24] Iodo lactone **15** would be expected to be the kinetically, and perhaps thermodynamically, preferred product, eq 2.



(2)

Completion of the preparation of **1** required conversion of the isopropenyl group to an amine functionality and olefin/ester regeneration from the iodo lactone. Ozonolysis of iodo lactone **15** afforded ketone **17**[25] in which the acetyl group is locked in a stable, equatorial position preventing epimerization. Conversion of **17** to **19** (2.9 equiv of NH_2OH·HCl, catalytic 4-(dimethylamino)pyridine, pyridine,[26a] 1.2 equiv of CH_3SO_2Cl,[26b] 1.8 equiv of Et_3N, CH_2Cl_2) and Beckmann rearrangement (SiO_2)[26] afforded the desired amide **20**. Treatment of amide **20** with zinc dust in hot ethanol[27] and esterification with excess diazomethane[28] afforded **1** in 90% yield. The C-4, C-9, and C-10 centers of **1** correspond to the required absolute configuration at the C-9, C-13, and C-14 centers of natural (–)-morphine.

Additional Studies. Amide **23** was prepared for comparison and unambiguous verification of the stereochemistry of racemic Δ^6-1-octalones prepared in the accompanying paper, eq 3. Treatment of **1** with benzoyl chloride and triethylamine in the presence of catalytic 4-(dimethylamino)pyridine (DMAP) afforded imide **22** (96%). Methanolysis of the imide **22** afforded nearly equal amounts of **23** and recovered **1**.



(3)

22, R^1 = $COCH_3$, R^2 = COPh

23, R^1 = H, R^2 = COPh

(a) PhCOCl, Et_3N, DMAP, CH_2Cl_2, **22** (96%).

(b) CH_3OLi, CH_3OH, **23** (49%) and **21** (45%).

Utilization of **1** in the preparation of morphine-related analgesics is in progress.

Experimental Section

Melting points were determined on a Hoover-Thomas melting point apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Beckman IR-33, a Beckman Acculab-3, a Perkin-Elmer Model 710B, or an IBM FTIR-32 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer. Electron impact mass spectra (EIMS), chemical

(22) Compound **12** was characterized: ^1H NMR ($CDCl_3$) δ 5.61 (br s, 2 H, CH=CH), 4.15 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.05–1.10 (m, 10 H), 2.20 (s, 3 H, $COCH_3$), 1.23 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$).

(23) (a) For the use of lithium methyl- and *n*-propylthiolates for dealkylations of esters, see: Kelly, T. R.; Dali, H. M.; Tsang, W. G.; *Tetrahedron Lett.* **1977**, 3859. Bartlett, P. A.; Johnson, W. S. *Ibid.* **1970**, 4459 (respectively). (b) House, H. O.; Haack, J. L.; McDaniel, W. C.; VanDerveer, D. *J. Org. Chem.* **1983**, *48*, 1643. (c) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365. Liotta, D.; Santiesteban, H. *Ibid.* **1977**, 4369. (d) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918. (e) Elsinger, F.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1960**, *43*, 113.

(24) (a) The iodo lactonization was run under kinetic conditions (KI, I_2, $NaHCO_3$, THF–H_2O). The reaction was not attempted under thermodynamic conditions (I_2, CH_3CN); see: Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (b) One isomer of iodo lactone **16** was isolated and the iodomethyl group was assumed to be equatorial. For a discussion of these and related topics; see ref 24a and Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. Compound **14** was regenerated from **16** (3 equiv of Zn, EtOH, 3 h, 70 °C, 80%).

(25) The use of catalytic OsO_4–$NaIO_4$ (5–7 equiv, dioxane–water, 25 °C, 3–6 days) afforded ketone **17** in 60–70% yield.

(26) (a) For oxime formation, see: Hill, R. K.; Conley, R. T.; Chortyk, O. T. *J. Am. Chem. Soc.* **1965**, *87*, 5646. (b) For oxime methanesulfonate formation, see: Hattori, K.; Matsumura, Y.; Miyazuki, T.; Maruoka, K.; Yamamoto, H. *Ibid.* **1981**, *103*, 7368. (c) For silica gel and alumina promoted Beckmann rearrangements, see: Craig, J. C.; Naik, A. R. *Ibid.* **1962**, *84*, 3410. Tamura, Y.; Fujiwara, H.; Sumoto, K.; Ikeda, M.; Kita, Y. *Synthesis* **1973**, 215.

(27) House, H. O.; Ro, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 182.

(28) De Boer, Th. T.; Backer, H. J. "Organic Syntheses"; John Wiley and Sons: New York, 1963; Collect. Vol. IV, p 250.

(29) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(30) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

ionization mass spectra (CIMS), and high-resolution mass spectra (HRMS) were obtained on a Varian CH-5 or a Ribermag R10-10 mass spectrometer by Charles Judson and Robert Drake. Microanalysis were performed by Tho I. Nguyen on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Medium-pressure liquid chromatography (MPLC)[31a] and flash chromatography[31b] were performed on silica gel 60 (230–400 mesh). Preparative centrifugal thin-layer chromatography (PCTLC)[31c] was performed on a Chromatotron Model 7924 (Harrison Research, Palo Alto, CA) on Kieselgel 60 PF_{254}/$CaSO_4 \cdot {}^1/_2\ H_2O$ (Merck, D-6100 Darmstadt, FRG). Ozone was generated with a Welsbach T-23 ozonator. All dry solvents were distilled under argon, nitrogen, or vacuum. Tetrahydrofuran (THF) and ether were distilled immediately before use from benzophenone ketyl. Benzene was distilled from benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide. Dioxane, xylenes, toluene, diisopropylamine, and hexamethylphosphoramide (HMPA) were distilled from powered calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Methanesulfonic acid was vacuum distilled. Ethanol and methanol were distilled from their respective magnesium alkoxides. Extraction and chromatographic solvents (methylene chloride, ethyl acetate, ether, pentane, and hexane) were distilled before use. Diisopropylethylamine was dried over neutral alumina. *p*-Toluenesulfonic acid and hydroxylamine hydrochloride were dried under vacuum in the presence of phosphorus pentoxide. All reactions requiring anhydrous conditions were run under positive pressure of argon and reagents were introduced by syringe through a septum. Syringes and reaction flasks for anhydrous reactions were oven dried. All other reactions were sealed from the atmosphere or run under positive pressure of nitrogen.

(1*R*,5*S*)-(+)-Nopinone (3). Pyridinium dichromate[16] (295 g, 0.847 mol, 3.1 equiv) was added in three equal portions over 15 min to a 5–10 °C solution of (1*R*,2*R*,5*S*)-(−)-*cis*-nopinol (**4**, 38.5 g, 0.275 mmol, 6x recrystallized) in dry acetone (2 L) stirred by an overhead mechanical stirrer. The resulting mixture was stirred at 5–10 °C for an additional 10 min then at 25 °C for 3 h before filtration through Celite (ether wash). The filtrate was concentrated in vacuo and passed through a plug of silica gel (13 × 10 cm, 25% ether–pentane eluant) to afford 36.0 g (38.0 g theoretical, 95%) of (+)-nopinone (**3**). A sample was distilled with a Kugelrohr apparatus (80 °C bath temperature (10–15 mmHg)) to give pure **3**: $[\alpha]^{22}_D$ +38.85° (*c* 4.0, methanol) [lit[8] $[\alpha]^{22}_D$ +39.0° (*c* 4, methanol), calcd $[\alpha]_D$ +39.9° (methanol)]; ^{1}H NMR[32] ($CDCl_3$) δ 2.60–1.40 (m, 8 H, aliphatic), 1.32 (s, 3 H, exo CH_3), 0.85 (s, 3 H, endo CH_3); IR (film) ν_{max} 2952, 1717 cm^{-1}.

(+)-Nopinone was also prepared by ozonolysis of (−)-β-pinene (**2**) as described below.

(1*R*,2*R*,5*S*)-(−)-*cis*-Nopinol (4). A stream of ozone/oxygen (ca. 5 L/min) was bubbled through a −78 °C solution of (1*S*,5*S*)-(−)-β-pinene[7a] (**2**, 103 g, 0.76 mol) in absolute methanol (200 mL) until a persistent blue color was observed (10 h). The reaction mixture was flushed with nitrogen and treated with dimethyl sulfide (200 mL) at −78 °C. The resulting mixture was allowed to warm to 25 °C over 3 h and stirred at 25 °C for an additional 11 h before dilution with water (200 mL). The mixture was extracted with hexane (5 × 100 mL) and the combined organic extracts were washed with water and saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo to give (+)-nopinone (**3**)[8] as a yellow oil.

The crude (+)-nopinone was dissolved in tetrahydrofuran (2.5 L) and treated with sodium borohydride (53 g, 1.4 mol) at 0 °C. Water (300 mL) was added dropwise over 1 h to the 0 °C solution and the resulting mixture was stirred at 25 °C for 18 h.[10a] The reaction mixture was diluted with ether (2 L) and the layers were separated. The aqueous layer was extracted with ether (2 × 100 mL) and the combined extracts were washed with water (2 × 500 mL) and saturated aqueous sodium chloride (300 mL), dried over sodium sulfate, and concentrated in vacuo. Recrystallization of the residue from hexane afforded 80 g (107 g theoretical, 75%) of **4** as a white, crystalline solid: $[\alpha]^{22}_D$ −9.23° (*c* 4.70, methanol). Three recrystallizations afforded 62 g (58%, 83% recovery) of **4**: $[\alpha]^{22}_D$ −9.28° (*c* 4.55, methanol). Six recrystallizations afforded 42 g (39%; 53% recovery) of **4**: mp 101–102 °C (lit.[33] mp 101.5–102 °C); $[\alpha]^{22}_D$ −9.33° (*c* 5.70, methanol), −5.51° (*c* 10.65, ether) [lit.[33] $[\alpha]^{23}_D$ −5.55° (*c* 10.62, ether)]; ^{1}H NMR[10a] ($CDCl_3$) δ 4.21 (m, 1 H, C*H*OH), 2.40–1.25 (m, 8 H), 1.21 (s, 3 H, exo CH_3), 1.10 (s, 3 H, endo CH_3), 0.87 (d, J = 9 Hz, 1 H, endo C-7 H); IR ($CHCl_3$) ν_{max} 3630, 3470, 1465, 1385, 1365, 1240, 1120, 1075, 1015, 980 cm^{-1}.

(1*S*,2*S*,5*R*)-(+)-*cis*-Nopinol. When the procedure for the preparation of (−)-*cis*-nopinol (**4**) was followed, (+)-β-pinene[15] (211 mg, 1.55 mmol) was converted to 109 mg (218 mg theoretical, 50%) of (1*S*,2*S*,5*R*)-(+)-*cis*-nopinol: mp 98–99 °C; $[\alpha]^{22}_D$ +9.53° (*c* 0.85, methanol); ^{1}H NMR ($CDCl_3$) δ 4.21 (m, 1 H, C*H*OH), 2.40–1.25 (m, 8 H), 1.21 (s, 3 H, exo CH_3), 1.10 (s, 3 H endo CH_3), 0.87 (d, J = 9 Hz, 1 H, endo C-7 H).

***O*-Acetylmandelate Ester of (−)-*cis*-Nopinol (5).** A 0 °C solution of dicyclohexylcarbodiimide (72.9 mg, 0.35 mmol, 1.26 equiv) in dry methylene chloride (0.3 mL) was added dropwise to a 0 °C solution of (*R*)-(−)-*O*-acetylmandelic acid[14a] (72.7 mg, 0.37 mmol, 1.34 equiv), (−)-*cis*-nopinol (**4**, 39.8 mg, 0.28 mmol, 1.34 equiv), and 4-(dimethylamino)pyridine (2.0 mg, 0.016 mmol, 0.06 equiv) in methylene chloride (0.7 mL) over 10 min. The resulting mixture was allowed to stir at 25 °C for 71 h. Additional *O*-acetylmandelic acid (77 mg, 0.40 mmol, 1.5 equiv) and dicyclohexylcarbodiimide (70 mg, 0.34 mmol, 1.2 equiv) were added to the 0 °C reaction mixture and stirred at 25 °C for 28 h. The reaction was filtered through Celite (methylene chloride wash), the filtrate was washed with 2.5% aqueous hydrochloric acid (8 mL), 5% aqueous sodium carbonate (8 mL), and saturated aqueous sodium chloride (8 mL), dried over sodium sulfate, and concentrated in vacuo.[14b] Flash chromatography (SiO_2, 1 × 11 cm, 10% ethyl acetate–hexane eluant) afforded 83.5 mg (89.8 mg, theoretical, 93%) of **5** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.38 (br s, 5 H, aromatic), 5.78 (s, 1 H, benzylic CH), 5.22 (m, 1 H), 2.45–1.50 (m, 7 H, aliphatic), 2.17 (s, 3 H, $OC(O)CH_3$), 1.04 (s, 3 H, exo CH_3), 0.93 (d, J = 10 Hz, 1 H, endo C-7 H), 0.74 (s, 3 H, endo CH_3); IR (film) ν_{max} 2948, 1744, 1372, 1233, 1215, 1055 cm^{-1}; EIMS, m/e 316 (M^+).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.80; H, 8.03.

***O*-Acetylmandelate Ester of (+)-*cis*-Nopinol (6).** A 0 °C solution of dicyclohexylcarbodiimide (32.8 mg, 0.159 mmol, 1.01 equiv) in dry methylene chloride (0.2 mL) was added to a 0 °C solution of (+)-*cis*-nopinol (22.2 mg, 0.158 mmol), (*R*)-(−)-*O*-acetylmandelic acid[14a] (31.6 mg, 0.163 mmol, 1.03 equiv), and 4-(dimethylamino)pyridine (1.1 mg, 0.008 mmol, 0.052 equiv) in methylene chloride (0.4 mL) over 5 min. The resulting mixture was stirred at 25 °C for 46 h and filtered through Celite (methylene chloride wash). The filtrate was washed with 5% aqueous hydrochloric acid (1 mL), 5% aqueous sodium carbonate (1 mL), and saturated aqueous sodium chloride (1 mL), dried over sodium sulfate and concentrated in vacuo.[14b] Flash chromatography (SiO_2, 1 × 15 cm, 15% ethyl acetate–hexane eluant) afforded 23.0 mg (50 mg theoretical, 46%, 90% based on recovered (+)-*cis*-nopinol) of **6** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 5 H, aromatic), 5.87 (m, 1 H, benzylic CH), 5.21 (m, 1 H), 2.50–1.35 (m, 7 H, aliphatic), 2.18 (s, 3 H, $OC(O)CH_3$), 1.19 (s, 3 H, exo CH_3), 0.95 (d, J = 10 Hz, 1 H, endo C-7 H), 0.87 (s, 3 H, endo CH_3); IR (film) ν_{max} 2950, 1746, 1371, 1275, 1217, 1180, 1061 cm^{-1}; EIMS, m/e 316 (M^+).

(1*R*,5*R*)-(+)-Ethyl 6,6-Dimethyl-2-oxobicyclo[3.1.1]hept-3-ene-3-carboxylate (7). A solution of (+)-nopinone (**3**, 13 g, 94 mmol) in dry tetrahydrofuran (70 mL) was added dropwise to a 0 °C slurry of sodium hydride (8.27 g of 60% in oil, 207 mmol, 2.2 equiv) in dry tetrahydrofuran (400 mL) and the resulting mixture was stirred until hydrogen evolution ceased. Diethyl carbonate (13.7 mL, 13.3 g, 112.8 mmol, 1.2 equiv) was added to the cold reaction mixture and the resulting mixture was stirred at 25 °C for 12 h before being poured onto saturated aqueous ammonium chloride. The resulting aqueous solution was extracted

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with ether (4×) and the combined organic extracts were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated in vacuo. Chromatography (SiO_2, 30% ether–hexane eluant) afforded 17.8 g (19.7 g theoretical, 90%) of the ethyl 6,6-dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate[17a] as a clear oil: ^1H NMR ($CDCl_3$) δ 11.91 (br s, C=COH), 4.25, 4.23, 4.21 (three q, 3H, trans/cis/enol $CO_2CH_2CH_3$), 3.31–3.30 (m, $CHCO_2Et$); IR (film) ν_{max} 2930, 1740, 1720, 1650, 1620, 1280 cm^{-1}; EIMS, *m/e* (relative intensity) 210 (M^+, 14), 195 (8), 149 (21), 121 (48), 109 (37), 95 (69), 83 (49), 55 (base).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.68.

Ethyl 6,6-dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate (10.3 g, 48.9 mmol) in dry tetrahydrofuran (50 mL) was added dropwise (30 min) to a 0 °C slurry of sodium hydride (2.35 g of 60% in oil, 58.8 mmol, 1.2 equiv) in tetrahydrofuran (80 mL) and the resulting mixture was stirred at 0 °C for 10 min. A freshly prepared solution of phenylselenenyl bromide[17b] (28.6 mmol, 1.2 equiv) in tetrahydrofuran (25 mL) was added over 10 min to the 0 °C solution of the β-keto ester enolate and the resulting mixture was stirred at 0 °C for 20 min and then at 25 °C for 30 min. The reaction was poured onto saturated aqueous sodium bicarbonate (150 mL), 50% ether–hexane (150 mL), and crushed ice (100 g). The layers were separated and the aqueous phase was extracted with 50% ether–hexane (3 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. MPLC (SiO_2, 25 × 1000 cm, 5% ether–hexane eluant) afforded 15.8 g (17.9 g theoretical, 88%) of ethyl 6,6-dimethyl-2-oxo-3-(phenylseleno)bicyclo[3.1.1]heptane-3-carboxylate as a white, crystalline solid: mp 67–69 °C (ethyl acetate–hexane); ^1H NMR ($CDCl_3$) δ 7.70 (m, 2 H, aromatic), 7.33 (m, 3 H, aromatic), 3.97 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.00–1.01 (m, 6 H, aliphatic) 1.35 (s, 3 H, CH_3), 1.18 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 0.98 (s, 3 H, CH_3); IR ($CHCl_3$) ν_{max} 2980, 1710, 1240, 1180, 1025 cm^{-1}; EIMS, *m/e* (relative intensity) 366–364 (M^+, 2/1, 7.8/4.3), 256 (22), 254 (13), 183 (31), 181 (27), 157 (24), 107 (34), 91 (40), 83 (54), 79 (30), 77 (54), 55 (96), 53 (26), 51 (23), 43 (33), 41 (base).

Anal. Calcd for $C_{18}H_{22}O_3Se$: C, 59.18; H, 6.07. Found: C, 59.57; H, 6.20.

Approximately 4 mL of a 15% aqueous hydrogen peroxide solution (40 mL, 185 mmol, 4.4 equiv) was added slowly to a 25 °C solution of the selenide (15.3 g, 41.9 mmol) in methylene chloride (160 mL). The reaction was immersed in an ice bath to maintain the reaction temperature at 20–30 °C. The remaining hydrogen peroxide solution (ca. 36 mL) was added over 15 min while the reaction temperature was maintained at 20–30 °C for 50 min.[17b] The mixture was poured onto a stirred mixture of aqueous 5% sodium bicarbonate (150 mL) and methylene chloride (150 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo to give 8.14 g (8.72 theoretical, 93%, 82% from ethyl 6,6-dimethyl-2-oxobicyclo[3.1.1]heptane-3-carboxylate) of the desired enone **7** as a clear oil: $[\alpha]^{22}_D$ +228.88° (*c* 2.68, methylene chloride); ^1H NMR ($CDCl_3$) δ 8.15 (m, 1 H, vinyl CH), 4.30 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 2.81 (m, 3 H, aliphatic), 2.15 (m, 1 H, aliphatic), 1.53 (s, 3 H, CH_3), 1.34 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.03 (s, 3 H, CH_3); IR (film) ν_{max} 2995, 1740, 1700, 1375, 1280, 1080 cm^{-1}; EIMS, *m/e* (relative intensity) 208 (M^+, 8), 193 (16), 162 (91), 147 (20), 134 (42), 121 (76), 120 (27), 119 (47), 107 (40), 106 (21), 105 (33), 93 (30), 92 (39), 91 (base), 79 (41), 65 (41), 55 (77); HRMS, *m/e* 208.1086, $C_{12}H_{16}O_3$ requires 208.1099.

(2*R*,4*S*,9*R*,10*S*)-(+)-3,3-Dimethyl-9-(ethoxycarbonyl)-2,4-methano-*cis*-Δ^6-1-octalone (8). Method A. 1,3-Butadiene (ca. 12 mL, 7.5 g, 140 mmol, 40 equiv) was condensed in a resealable, glass tube[34] (2.5 × 22 cm) containing a −78 °C solution of enone **7** (760 mg, 3.65 mmol) in dry xylenes (6 mL). The reaction vessel was warmed at 120 °C for 32 h in a steel pipe. The reaction vessel was slowly cooled to −78 °C and unsealed and the monomeric 1,3-butadiene was removed under a stream of nitrogen at 25 °C. The resulting residue was passed through a plug of silica gel (3.5 × 5 cm, hexane eluant) to remove polymeric 1,3-butadiene. MPLC (SiO_2, 15 × 1000 mm, 5% ether–hexane eluant) afforded 781 mg (957 mg theoretical, 82%) of **8** as a white solid: mp 60–61 °C (hexane); $[\alpha]^{25}_D$ +87.25° (*c* 2.37, methanol); ^1H NMR ($CDCl_3$) δ 5.86 (m, 2 H, CH=CH), 4.22 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.30–1.01 (m, 9 H, aliphatic), 1.36 (s, 3 H, CH_3), 1.27 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 1.01 (s, 3 H, CH_3); IR ($CHCl_3$) ν_{max} 2975, 1700, 1195 cm^{-1}; EIMS, *m/e* (relative intensity) 262 (M^+, 1), 189 (19), 152 (19), 147 (20), 144 (18), 133 (22), 105 (31), 95 (base), 91 (44), 83 (base), 55 (71).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.01; H, 8.70.

In addition, 3,3-dimethyl-2,4-methano-Δ^6-1-octalone was isolated in 3% yield (24 mg): ^1H NMR ($CDCl_3$) δ 5.77 (m, 2 H, CH=CH), 2.60–1.35 (m, 10 H, aliphatic), 1.37 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3); EIMS, *m/e* (relative intensity) 190 (M^+, 8), 175 (5), 147 (5), 121 (25), 107 (10), 105 (11), 95 (18), 93 (13), 91 (29), 86 (45), 84 (76), 83 (base), 79 (24), 77 (20), 55 (39).

Method B. 1,3-Butadiene (ca. 4 mL, 2.6 g, 48 mmol, 37 equiv) was added rapidly to a solution of the enone **7** (271 mg, 1.3 mmol), 0.5 mL of 0.027 M copper(II) tetrafluoroborate/methylene chloride[18] (0.0014 mmol, 0.01 equiv) in dry methylene chloride (1.5 mL) in a 200-mL Wheaton pressure bottle, and the resulting solution was stirred at 25 °C for 12 h. Chromatography (SiO_2, 1.5 × 17 cm, 5% ether–hexane eluant) afforded 105 mg (304 mg theoretical, 34%) of the desired product **8** which was identical with that prepared in Method A.

(4*R*,9*R*,10*S*)-(+)-9-(Ethoxycarbonyl)-4-(2-propenyl)-*cis*-Δ^6-1-octalone (10) and 11. Boron tribromide (0.44 mL, 1.17 g, 4.65 mmol, 1.20 equiv) was added rapidly to a −93 °C solution of **8** (1.01 g, 3.87 mmol) in dry methylene chloride (11 mL) under argon.[19] The reaction mixture was stirred at −100 to −93 °C for 40 min before quenching with dry methanol (1.71 mL, 1.35 g, 42.3 mmol, 9.10 equiv) and the mixture stirred at low temperature for 5 min. The resulting mixture was poured onto water (60 mL) and the aqueous mixture was extracted with ether (6 × 25 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (20 mL), dried over sodium sulfate, and concentrated in vacuo. The resulting yellow oil was *very rapidly* passed through a short plug of neutral alumina (1.5 × 1.5 cm, ether eluant) to give 1.31 g (1.33 g theoretical, 98%) of the bromide **9** as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 5.58 (m, 2 H, CH=CH), 4.17 (m, 2 H, $CO_2CH_2CH_3$), 3.00–1.40 (m, 10 H, aliphatic), 1.88 (s, 3 H, CH_3), 1.83 (s, 3 H, CH_3), 1.25 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$); IR (film) ν_{max} 3000, 1720, 1460, 1395, 1375, 1250, 1220 cm^{-1}.

A solution of the bromide **9** (1.31 g, 3.81 mmol) and diisopropylethylamine (0.54 g, 4.17 mmol, 1.12 equiv) in dry dioxane (17 mL) was warmed at 60–65 °C for 66 h under nitrogen. The cooled reaction mixture was poured over aqueous 0.5% hydrochloric acid (80 mL) and the resulting mixture was extracted with ether (5 × 25 mL). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. MPLC (SiO_2, 15 × 1000 mm, 10% ether–hexane eluant) gave 626 mg (1.01 g theoretical, 62%) of the isopropenyl product **10** as a white solid: mp 59.5–60.5 °C (distilled bulb to bulb at 120 °C bath temperature (0.8 mmHg)); $[\alpha]^{23}_D$ +174.9° (*c* 3.38, methanol); ^1H NMR ($CDCl_3$) δ 5.62 (m, 2 H, CH=CH), 4.83 (br s, 2 H, $R_2C=CH_2$), 4.24 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.00–1.50 (m, 10 H, aliphatic), 1.68 (s, 3 H, CH_3), 1.27 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$); IR (KBr) ν_{max} 2932, 1740, 1707, 1431, 1215 cm^{-1}; EIMS, *m/e* (relative intensity) 262 (M^+, 4), 217 (3), 216 (6), 152 (73), 151 (55), 120 (60), 105 (76), 91 (61), 79 (base), 77 (base), 69 (86).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.48. Found: C, 73.00; H, 8.80.

The isopropylidene derivative **11** was also isolated as an oil (302 mg, 30%) and characterized: ^1H NMR ($CDCl_3$) δ 5.61 (m, 2 H, CH=CH), 4.15 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.58 (dd, J = 10, 6 Hz, 1 H, C-10 H), 3.00–1.00 (m, 8 H aliphatic), 1.79 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 1.21 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$); IR (film) ν_{max} 2910, 1710, 1430, 1225, 1035 cm^{-1}; EIMS, *m/e* (relative intensity) 262 (M^+, 42), 261 (2), 217 (16), 209 (22), 208

(34) The reaction was run in a thick-walled, glass tube internally threaded on one end and sealed under argon with a solid threaded teflon plug. The reaction vessel was fabricated from a chromatography column purchased from Ace Glass Company.

(base), 193 (34), 189 (63), 105 (45), 91 (74), 77 (50).

(4*R*,9*R*,10*S*)-(+)-9-(Ethoxycarbonyl)-4-(2-propenyl)-*cis*-Δ^6-1-octalone Ethylene Ketal (13). A solution of ketone **10** (1.20 g, 4.58 mmol), ethylene glycol (0.51 mL, 0.57 g, 9.14 mmol, 2.0 equiv), and *p*-toluenesulfonic acid (39 mg, 0.23 mmol, 0.05 equiv) in dry benzene (55 mL) was warmed at reflux with azeotropic removal of water for 6 h. The reaction was cooled to 25 °C and concentrated in vacuo. MPLC (SiO_2, 25 × 500 mm, 20% ether–hexane eluant) gave 1.27 g (1.40 g theoretical, 91%) of the desired ketal **13** as a colorless oil. A sample was distilled (bulb to bulb, 120 °C bath temperature (1 mmHg)): $[\alpha]^{23}_D$ +39.7° (*c* 3.19, methanol); ^{1}H NMR ($CDCl_3$) δ 5.54 (m, 2 H, CH=CH), 4.74 (m, 2 H, $R_2C{=}CH_2$), 4.15 (q, J = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.86 (m, 4 H, ethylene ketal), 3.10–1.40 (m, 10 H, aliphatic), 1.66 (s, 3 H, CH_3), 1.24 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$); IR (film) ν_{max} 2934, 1723, 1263, 1194, 1089 cm^{-1}; EIMS, *m/e* (relative intensity) 306 (M^+, 4), 233 (2), 155 (9), 154 (11), 99 (base), 86 (66), 79 (13), 77 (14), 55 (19).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.50; H, 8.90.

(4*R*,9*R*,10*S*)-9-Carboxy-4-(2-propenyl)-*cis*-Δ^6-1-octalone Ethylene Ketal (14). The ester **13** (535.1 mg, 1.75 mmol) was added to 17.5 mL of 0.5 M lithium ethylthiolate in hexamethylphosphoramide (8.75 mmol, 5.0 equiv) and the resulting solution was warmed at 100 °C for 2.5 h under argon.[23a] The cooled reaction mixture was poured onto water (200 mL), crushed ice (200 g), and ethyl acetate (120 mL). The resulting mixture was acidified with aqueous 5% hydrocholoric acid while stirring and the layers were immediately separated. The cold, aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous lithium chloride (3 × 100 mL), dried over sodium sulfate, and concentrated in vacuo. MPLC (SiO_2, 25 × 250 mm, 500 mL of 20% ether–20% methylene chloride–hexane eluant, 50% ethyl acetate–hexane eluant) afforded 442 mg (487 mg theoretical, 91%) of the carboxylic acid **14** as a white solid: mp 161–162 °C (ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$) δ 10.75 (br s, 1 H, CO_2H), 5.56 (m, 2 H, CH=CH), 4.74 (br s, 2 H, $R_2C{=}CH_2$), 3.93 (s, 4 H, ethylene ketal), 3.00–1.25 (m, 10 H, aliphatic), 1.63 (s, 3 H, CH_3); IR ($CHCl_3$) ν_{max} 3700–2500, 2950, 1695, 1445, 1140, 1090 cm^{-1}; EIMS, *m/e* (relative intensity) 278 (M^+, 3), 233 (1), 155 (15), 154 (15), 99 (55), 87 (12), 86 (base), 79 (12), 77 (13), 55 (13).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.00; H, 8.02.

(+)-Iodo Lactone 15. A solution of the carboxylic acid **14** (790 mg, 2.84 mmol) in tetrahydrofuran–water (22 mL of 3:1) at 0 °C was treated with sodium bicarbonate (1.67 g, 19.9 mmol, 7.0 equiv) and the resulting mixture was stirred at 0 °C for 15 min. A mixture of potassium iodide (571 mg, 3.44 mmol, 1.2 equiv) and iodine (2.16 g, 8.52 mmol, 3.0 equiv) in water (15 mL) was added to the reaction at 0 °C and the resulting mixture was stirred at 25 °C for 20 h.[23b,24a] The reaction was poured onto 10% aqueous sodium thiosulfate (50 mL) and the resulting aqueous solution was extracted with ether (4 × 30 mL). The combined organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated in vacuo. MPLC (SiO_2, 25 × 250 mm, 30% ether–hexane eluant) gave 990 mg (1.15 g theoretical, 86%) of the desired lactone **15** as a white solid: mp 119–120 °C (hexane); $[\alpha]^{28}_D$ +27.62° (*c* 1.58, methanol); ^{1}H NMR ($CDCl_3$) δ 4.97 (m, 2 H, $R_2C{=}CH_2$), 4.75 (m, 1 H, CHO), 4.30 (m, 1 H, CHI), 3.49 (m, 4 H, ethylene ketal CH_2's), 3.05–1.20 (m, 10 H, aliphatic), 1.63 (m, 3 H, CH_3); IR ($CHCl_3$) ν_{max} 2965, 1780, 1165, 1065, 945 cm^{-1}; EIMS, *m/e* (relative intensity) 404 (M^+, 0.3), 277 (0.3), 154 (1), 153 (3), 149 (2), 128 (2), 99 (base), 86 (18).

Anal. Calcd for $C_{16}H_{21}IO_4$: C, 47.54; H, 5.25. Found: C, 47.68; H, 5.39.

The six-membered iodo lactone[24b] **16** was isolated in 12% yield (133 mg): ^{1}H NMR ($CDCl_3$) δ 5.63 (m, 2 H, CH=CH), 3.95 (m, 4 H, ethylene ketal CH_2's), 3.43 (s, 2 H, CH_2I), 2.75–1.25 (m, 10 H, aliphatic), 1.70 (s, 3 H, CH_3); EIMS, *m/e* (relative intensity) 404 (M^+, 2), 281 (1), 251 (2), 99 (base), 91 (9), 86 (20), 79 (11), 77 (11), 55 (11).

(+)-Ketone 17. A stream of ozone–oxygen (0.8 L/min) was passed through a −78 °C solution of the iodo lactone **15** (405.0 mg, 1.0 mmol) in absolute methanol (40 mL) for 6 min. The ozonide precipitated from the reaction. A stream of nitrogen was passed through the reaction mxiture until the blue color disappeared. Dimethyl sulfide (2.0 mL) was added to the reaction mixture at −78 °C and allowed to slowly warm to 25 °C over 3 h and then stirred at 25 °C for 12 h. The solution was concentrated in vacuo and MPLC (SiO_2, 15 × 250 mm, 25% ethyl acetate–hexane eluant) gave 374.9 mg (407.0 mg theoretical, 92%) of the ketone **17** as a white solid: mp 131–135.5 °C (ethyl acetate–hexane); $[\alpha]^{23}_D$ −0.33° and $[\alpha]^{23}_{365}$ +66.99° (*c* 1.53, methanol); ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 1 H, CHO), 4.33 (m, 1 H, CHI), 3.98 (m, 4 H, ethylene ketal CH_2's), 3.00–1.45 (m, 10 H, aliphatic), 2.27 (s, 3 H, $COCH_3$); IR ($CHCl_3$) ν_{max} 2970, 1785, 1710, 1170, 1065 cm^{-1}; CIMS (NH_3), *m/e* (relative intensity) 407 (M^+ 1, 36), 363 (11), 279 (10), 100 (11), 99 (base), 86 (14).

Anal. Calcd for $C_{15}H_{19}IO_5$: C, 44.35; H, 4.71. Found: C, 44.71, H, 4.91.

(+)-Iodo Lactone Amide 20. 4-(Dimethylamino)pyridine (3.4 mg, 0.028 mmol, 0.06 equiv) was added to a 25 °C solution of the ketone **17** (186.7 mg, 0.46 mmol), hydroxylamine hydrochloride (93.0 mg, 1.34 mmol, 2.9 equiv), absolute methanol (0.6 mL), and dry pyridine (0.6 mL). The resulting mixture was stirred at 25 °C under argon for 18 h and poured onto a mixture of 5 g of crushed ice, 10 mL of 5% aqueous hydrochloric acid, and 5 mL of methylene chloride.[26a] The layers were separated and the cold, aqueous solution was extracted with methylene chloride (5 × 5 mL). The combined extracts were dried over sodium sulfate and concentrated in vacuo to give the oxime **18** as a white foam: ^{1}H NMR ($CDCl_3$) δ 8.40 (m, 1 H, OH), 4.75 (m, 1 H, CHO), 4.31 (m, 1 H, CHI), 3.98 (m, 4 H, ethylene ketal CH_2's), 3.05–1.65 (m, 10 H, aliphatic), 1.84 (s, 3 H, CH_3); IR ($CHCl_3$) ν_{max} 3600, 3300, 1780, 1165, 1065 cm^{-1}; CIMS (NH_3), *m/e* (relative intensity) 422 (M^+ 1, 71), 405 (2), 404 (10), 100 (7), 99 (base), 86 (6).

A −20 °C solution of the crude oxime **18** in dry methylene chloride (3.4 mL) under argon was treated sequentially with triethylamine (83 mg, 0.83 mmol, 1.8 equiv) and methanesulfonyl chloride (68 mg, 0.60 mmol, 1.3 equiv). The resulting solution was stirred at −20 to −15 °C for 1 h and poured onto 15 g of crushed ice and water. The aqueous mixture was extracted with methylene chloride (6 × 6 mL).[26b] The combined extracts were dried over sodium sulfate and concentrated in vacuo to give the oxime *O*-methanesulfonate **19** as a white foam: ^{1}H NMR ($CDCl_3$) δ 4.78 (m, 1 H, CHO), 4.30 (m, 1 H, CHI), 3.98 (m, 4 H, ethylene ketal CH_2's), 3.18 (s, 3 H, OSO_2CH_3), 3.05–1.65 (m, 10 H, aliphatic), 2.02 (s, 3 H, CH_3).

The crude oxime *O*-methanesulfonate **19** in chloroform (2 mL) was applied to a flash chromatography column (SiO_2, 1.5 × 19 cm, chloroform) and 18 mL of chloroform was passed through the column, and then after 42 h 10 mL of chloroform was passed through the column. The column was eluted (100 mL of 50% ethyl acetate–hexane eluant, 150 mL of 10% tetrahydrofuran–ethyl acetate eluant) at 54 h to give 163.3 mg (193.5 mg theoretical, 84%) of the amide **20** as a whte solid: mp 194–196 °C (ethyl acetate–hexane); $[\alpha]^{25}_D$ +7.62° and $[\alpha]^{25}_{365}$ +34.86° (*c* 0.525, methanol); ^{1}H NMR ($CDCl_3$) δ 5.05 (m, 1 H, NH), 4.75 (m, 1 H, CHO), 4.30 (m, 1 H, CHI), 3.95 (m, 4 H, ethylene ketal CH_2's, overlapping m, 1 H, NCH), 3.08–1.25 (m, 9 H, aliphatic), 2.01 (s, 3 H, $NCOCH_3$); IR (KBr) ν_{max} 3345, 1771, 1673, 1541, 1174, 1064 cm^{-1}; CIMS (NH_3), *m/e* (relative intensity) 422 (M^+ + 1, 95), 362 (40), 235 (8), 99 (base).

Anal. Calcd for $C_{15}H_{20}INO_5$: C, 42.77; H, 4.78; N, 3.33. Found: C, 43.14; H, 5.04; N, 3.50.

(4*R*,9*R*,10*R*)-(+)-4-(Acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone Ethylene Ketal (1). A mixture of the iodo lactone amide **20** (101.0 mg, 0.24 mmol), activated zinc dust[35] (47.6 mg, 0.728 mmol, 3.03 equiv), and absolute ethanol (1.0 mL) was warmed at 70 °C under argon with vigorous stirring for 1.25 h. The reaction mixture was cooled to ambient temperature and filtered through Celite (methanol wash), and the resulting filtrate was concentrated in vacuo to give a white solid. The crude carboxylate salt was suspended in methanol (1 mL), cooled to 0 °C, and treated with excess diazomethane[28] (ca. 20 equiv) in 5 mL of ether, and the resulting mixture was stirred at 0–25 °C for 3 h. The excess diazomethane was removed under

(35) Zinc dust was activated by washing with 5% aqueous hydrochloric acid (3x), water (3x), methanol (3x), and ether (3x) was dried under vacuum; see: Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.

a stream of nitrogen and the remaining solvent removed in vacuo. Chromatography (SiO_2, 1 × 6 cm, 10% tetrahydrofuran–ethyl acetate eluant) afforded 66.7 mg (74.2 mg theoretical, 90%) of **1** as a white foam. Recrystallization from ethyl acetate–hexane gave **1** as white needles: mp 188–189 °C; $[\alpha]^{25}_D$ −15.95° (*c* 1.56, methanol); ^{1}H NMR ($CDCl_3$) δ 6.01 (m, 1 H, NH), 5.50 (m, 2 H, CH=CH), 3.76 (m, 4 H, ethylene ketal CH_2's, overlapping m, 1 H, NCH), 3.60 (s, 3 H, CO_2CH_3), 3.05–1.25 (m, 9 H, aliphatic), 1.92 (s, 3 H, $NCOCH_3$); IR ($CHCl_3$) ν_{max} 3450, 3380, 3005, 2960, 1720, 1660, 1265, 1190 cm^{-1}; EIMS, *m/e* (relative intensity) 309 (M^+, 4), 250 (23), 191 (9), 99 (30), 87 (13), 86 (base), 77 (20), 56 (14).

Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.90; H, 7.50; N, 4.34.

(4*R*,9*R*,10*R*)-4-(*N*-Benzoyl-*N*-acetylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone Ethylene Ketal (22). Benzoyl chloride (12 μL, 14.5 mg, 0.103 mmol, 5.3 equiv) was added to a 25 °C solution of triethylamine (19 μL, 13.8 mg, 0.136 mmol, 7.0 equiv), 4-(dimethylamino)pyridine (0.05 equiv), and the acetylamide **1** (6.0 mg, 0.019 mmol) in dry methylene chloride (150 μL) and the resulting mixture was stirred at 25 °C for 15 h.[29] The reaction was quenched with saturated aqueous ammonium chloride (1 mL) and the resulting mixture was extracted with ethyl acetate (5 × 1 mL). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 6 cm, 40% ethyl acetate–hexane eluant) gave 7.5 mg (7.9 mg theoretical, 96%) of the imide **22** as a solid: ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 5 H, aromatic), 5.50 (m, 1 H, CH=CH), 3.84 (m, 4 H, ethylene ketal CH_2's; overlapping m, 1 H, NCH), 3.68 (s, 3 H, CO_2CH_3), 3.05–1.60 (m, 12 H, aliphatic); IR ($CHCl_3$) ν_{max} 3040, 1725, 1700 (shoulder), 1660, 1240 cm^{-1}; EIMS, *m/e* (relative intensity) 413 (M^+, 0.04), 371 (0.05), 273 (0.05), 272 (0.05), 250 (22), 105 (96), 99 (45), 86 (base), 77 (87), 43 (38).

(4*R*,9*R*,10*R*)-4-(Benzoylamino)-9-(methoxycarbonyl)-*cis*-Δ^6-1-octalone Ethylene Ketal (23) and 1. A solution of 2.0 M lithium methoxide in methanol (15 μL, 0.030 mmol, 1.7 equiv) was added to a 0 °C solution of the imide **22** (7.5 mg, 0.0018 mmol) in dry methanol (325 μL). The resulting mixture was stirred at 0–25 °C for 4 h and quenched with saturated aqueous ammonium chloride (1.5 mL).[30] The aqueous solution was extracted with ethyl acetate (6 × 1 mL), and the combined extracts were dried over sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 6 cm, 25 mL of 60% ethyl acetate–hexane, then 25 mL of 30% tetrahydrofuran–ethyl acetate eluant) afforded 3.3 mg (6.7 theoretical, 49%) of the benzoylamide **23** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2 H, aromatic), 7.43 (m, 3 H, aromatic), 5.88–5.45 (m, 3 H, CH=CH/NH), 4.10 (m, 1 H, NCH), 3.87 (m, 4 H, ethylene ketal), 3.70 (s, 3 H, CO_2CH_3), 3.10–1.50 (m, 9 H, aliphatic); IR ($CHCl_3$) ν_{max} 3450, 3010, 2960, 1720, 1655, 1510, 1265, 1200, 740, 660 cm^{-1}; EIMS, *m/e* (relative intensity) 371 (M^+, 5), 259 (5), 250 (12), 122 (63), 105 (base), 86 (27), 77 (55), 57 (12), 51 (17); HRMS, *m/e* 371.1734, $C_{21}H_{25}NO_5$ requires 371.1731.

Acetylamide **1** was isolated in 45% (2.5 mg, 5.6 mg theoretical) and was identical with original material prepared as described above.

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Regioselectivity of the Intermolecular Diels–Alder Reaction of Acyl Nitroso Compounds (*C*-Nitrosocarbonyl Compounds) and Nitrosoformates (*O*-Nitrosocarbonyl Compounds). Preparation of Functionalized *cis*-Δ^6-1-Octalones

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A study of the regioselectivity of the intermolecular Diels–Alder reaction of (nitrosocarbonyl)benzene and methyl nitrosoformate with representative electron-rich and electron-deficient 2-substituted 1,3-cyclohexadienes is described. The observed results are consistent with the prediction that nitrosocarbonyl compounds behave as dependable electron-deficient 2π components in a normal ($HOMO_{diene}$ controlled) Diels–Alder reaction with electron-rich 2-substituted dienes and additionally illustrate that they may serve as useful 2π components in regioselective Diels–Alder reactions with electron-deficient 2-substituted 1,3-cyclohexadienes. The latter results are consistent with either a normal ($HOMO_{diene}$ controlled) or inverse electron demand ($LUMO_{diene}$ controlled) Diels–Alder reaction. Utilization of the nitrosocarbonyl Diels–Alder adducts in a stereospecific preparation of functionalized, *cis*-Δ^6-1-octalones is detailed. In contrast to predictions based on secondary orbital control (allylic axial heteroatom orbital control), [4 + 2] cycloaddition of butadiene with the 5- and 6-substituted *N*-benzoyl 3-aza-2-oxobicyclo[2.2.2]oct-5-enes occurs on the face bearing the RCON–O bridge.

The orientation of the intermolecular Diels–Alder addition of aryl nitroso compounds with dienes has been investigated in detail and a rationalization of the observed regioselectivity has been presented based on the consideration of the relative stabilization of the two possible dipolar transition states.[2,3] The predicted and observed distal (ortho)[3] adduct in the cycloaddition of nitrosobenzene with isoprene is shown in eq 1. By contrast, a study of regioselectivity of the addition of nitrosobenzene with β-myrcene, a 2-alkyl-substituted 1,3-butadiene, re-

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