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APPLICATIONS OF THE INTRAMOLECULAR DIELS–ALDER REACTIONS OF HETERODIENES TO THE SYNTHESES OF INDOLE ALKALOIDS

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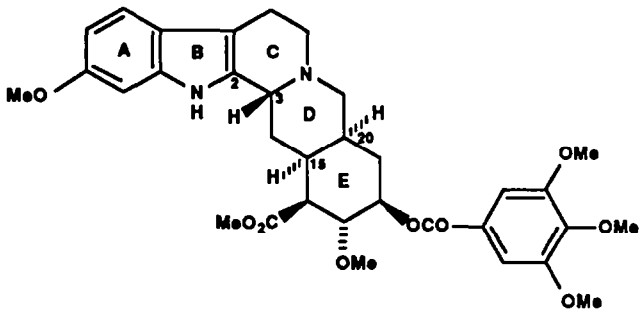
Abstract—A novel intramolecular Diels–Alder reaction involving the addition of an α,β-unsaturated aldehyde to an electron-deficient, dienophilic partner has been exploited as the key step in the development of a general entry to the heteroyohimboid and corynantheioid alkaloids. Thus, the thermal cyclization of the nitrogen-linked triene **11**, which is readily available in eight steps from propargyl alcohol, proceeded smoothly to afford the *cis*-cycloadduct **20** in 73% yield. The *cis*-lactam **20** serves the dual role of being the pivotal intermediate for the preparation of the secondary amine **24** (13 steps and 18% overall yield from propargyl alcohol), a known precursor of tetrahydroalstonine (**4**) and other heteroyohimboid bases, as well as for the syntheses of the α,β-unsaturated 2-piperidones **27** and **29**, model compounds that have been designed to test the feasibility of a new strategy for the synthesis of the corynantheioid alkaloids bearing an (*E*)-ethylidene moiety at C(20).

INTRODUCTION

The design and development of general strategies for the syntheses of alkaloid natural products have been a major focus of research in our laboratories, and the considerable challenge of inventing a new entry to the structurally diverse alkaloids belonging to the indole family[1] emerged as an intriguing objective. Of particular interest were the monoterpenoid-derived indole alkaloids of the yohimbane, heteroyohimbane and corynantheine types, some representative members of which include reserpine (**1**),[2] yohimbine (**2**),[3] α-yohimbine (**3**),[4] tetrahydroalstonine (**4**),[5] ajmalicine (**5**)[5] and geissoschizine (**6**).[6]

Historically, the synthetic approach to these naturally-occurring bases has typically involved the prior construction of a functionalized D/E or D-ring subunit or precursor thereof, which was then coupled with the requisite tryptophyl synthon to afford a 2,3-*seco*-derivative of the targeted alkaloid. Subsequent formation of the C-ring was achieved via generation of



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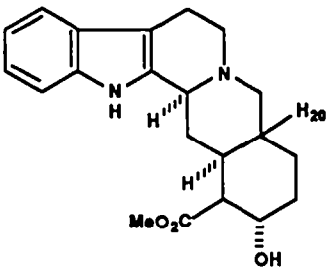
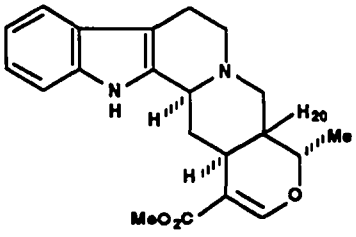
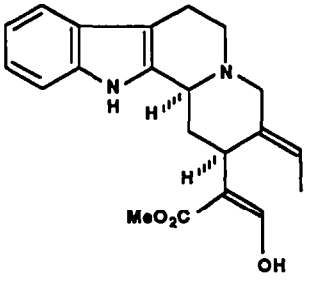


2: β-H_{20}; α-CO_2Me
3: α-H_{20}; β-CO_2Me



4: α-H_{20}
5: β-H_{20}



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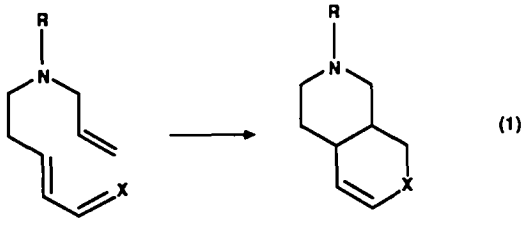
an electrophilic center at C(3) followed by cyclization onto the 2-position of the indole moiety. Since this tenet has proven to be fundamentally sound, the task of designing alternative entries to the yohimboid alkaloids may be formulated as a problem in the development of methodology for the construction of suitably substituted hydroisoquinolines, whereas access to the heteroyohimboid and corynantheioid bases may be framed as an exercise in the design of techniques for the formation of functionalized 7-oxahydroisoquinolines and substituted piperidines.

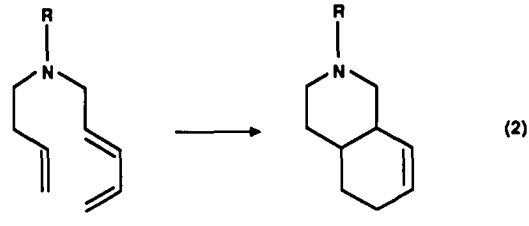
In conjunction with an ongoing program involving applications of intramolecular Diels–Alder[7] reactions for the assemblage of fused heterocyclic ring systems, it occurred to us that such a process might constitute an appealing solution to the problem at hand. For example, the cyclizations of trienes such as **7** and **9** (Eqs 1 and 2) in which the dienic and dienophilic partners are linked by a nitrogen atom should lead to fused, functionalized piperidine derivatives of the general types **8** and **10**, respectively. Although at the outset of these studies there had been numerous reports of intramolecular [4 + 2] cycloadditions to form hydroindoles, hydroisoindoles, hydroquinolines, indolizidines and quinolizidines,[8] there were few accounts of the production of hydroisoquinolines by such processes.[9] However, subsequent investigations in our laboratory have established that thermolyses of the trienes **7** (X = CH_2) and **9** proceed to give the hydroisoquinolines **8** (X = CH_2) and **10**, respectively,



(1)

7 **8**

X = CH_2
X = O



(2)

9 **10**

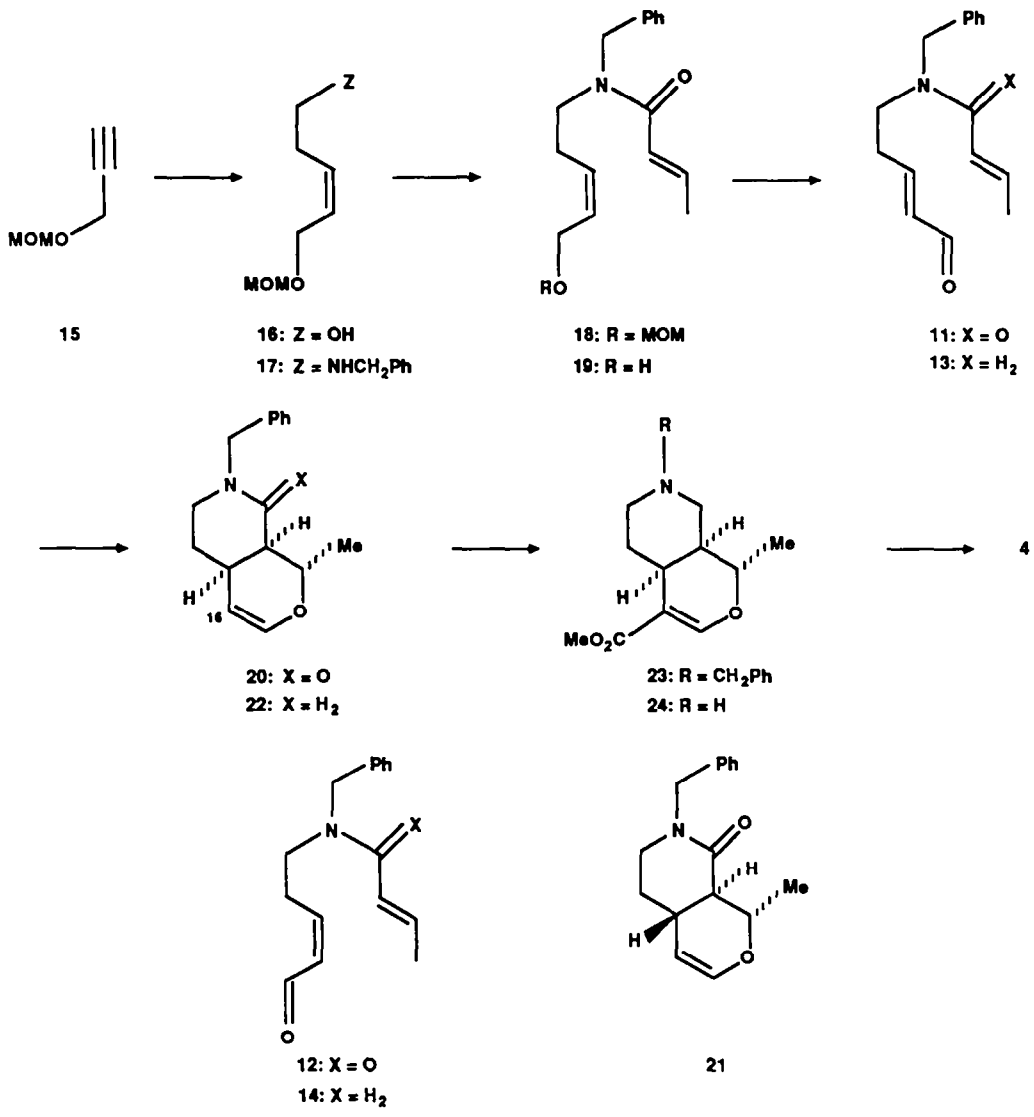
and a cyclization related to that depicted in Eq. (2) has recently been exploited as a key step in the total syntheses of the yohimboid alkaloids reserpine (**1**)[2d] and α-yohimbine (**3**).[4c]

The natural sequel to these investigations was to ascertain whether nitrogen-linked trienes in which the diene was an α,β-unsaturated aldehyde such as **7** (X = O) would undergo cyclization to afford 7-oxahydroisoquinolines **8** (X = O) since such compounds might be refunctionalized to provide facile access to the heteroyohimboid and corynantheioid alkaloids. Although the intermolecular Diels–Alder reactions of α,β-unsaturated carbonyl compounds with electron-rich, dienophilic partners to give dihydropyrans are extensively documented,[10,11] the related intramolecular reactions are not well established. Typically such reactions have involved the [4 + 2] cycloadditions of rather special dienes such as *o*-quinomethides[12] and 1,1-diacyl olefins[13] to carbon–carbon double bonds, and to our knowledge there is only one example of the cyclization of a triene in which an α,β-unsaturated aldehyde served as the dienic partner.[14] The summary of our recent investigations in the area of intramolecular, hetero-Diels–Alder reactions of trienes related to **7** (X = O) and the application of one such process to the synthesis of the heteroyohimboid and corynantheioid alkaloids constitute the substance of the present report.[15]

RESULTS AND DISCUSSION

One might envisage that the cycloadducts obtained upon the thermal cyclization of any of the α,β-unsaturated aldehydes **11–14** could lead to 7-oxahydroisoquinolines that could be elaborated into indole alkaloids of the heteroyohimbine and corynantheine families. However, based upon previous work[9] we anticipated that the cyclizations of the acrylamide derivatives **11** and **12** would proceed with a higher degree of stereoselectivity than those of the corresponding amines **13** and **14**, and hence initial efforts were directed towards their preparation.† In the event, deprotonation of the protected propargyl alcohol **15** with n-butyllithium and reaction of the resulting acetylide anion with ethylene oxide gave an intermediate acetylenic alcohol, which was smoothly reduced to the *Z*-homoallylic alcohol **16** by catalytic semi-hydrogenation (Scheme 1). Interchange of the hydroxyl group for the N-benzylamino group was conveniently achieved by treating the derived tosylate with benzylamine in DMSO in the presence of a catalytic amount of sodium iodide. Acylation of the secondary amine **17** with the mixed anhydride that was produced upon the reaction of crotonic acid with ethyl chloroformate in the presence of triethylamine proceeded without event to deliver the crotonamide **18**, and subsequent removal of the methoxymethyl hydroxyl protecting group by acid-catalyzed transketalization then provided the allylic alcohol **19**. Swern oxidation[16] of the allylic alcohol **19** gave the *Z*-α,β-unsaturated aldehyde **12**, which underwent facile acid-catalyzed isomerization to generate the corresponding *E*-isomer **11**. Interestingly, the double bond in **12** proved to be remarkably susceptible to $Z \rightarrow E$ isomerization, a reaction that appears to require acid or Lewis acid catalysis and is presumably facilitated by the proximate amide carbonyl function. For example, treatment of **19** with manganese dioxide or pyridinium dichromate,[17] reagents which are generally known to oxidize *Z*-allylic

† Owing to the apparent instability of the tertiary α,β-unsaturated amino aldehyde **14**, all attempts to effect its synthesis by oxidation of the corresponding allylic amino alcohol, which may be readily prepared, were frustrated by extensive decomposition and by the formation of numerous side products.



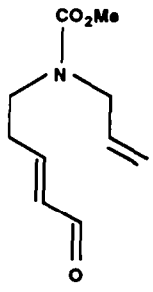
Scheme 1.

alcohols without concomitant isomerization to the *E*-olefin, afforded as the sole product the unsaturated aldehyde **11**, albeit in lower yields than the Swern oxidation/isomerization sequence.

The feasibility of exploiting the intramolecular hetero-Diels–Alder reaction as a novel and expeditious entry to the *cis*-D/E ring subunit of the heteroyohimbane alkaloids was then convincingly established by the thermolysis (190°) of **11**, a reaction which proceeded smoothly to deliver as a readily separable mixture (*ca* 5 : 1) the desired *cis*-cycloadduct **20**, which was isolated in 73% yield, together with the corresponding *trans*-cycloadduct **21**. A preliminary attempt to catalyze the reaction by the use of Lewis acids such as boron trifluoride etherate was unsuccessful. Although there was reason to believe that the *Z*-α,β-unsaturated aldehyde **12** would undergo the [4+2] cycloaddition to give the *cis*-lactam **20** with an even higher degree of stereoselectivity,[18] **12** underwent considerable decomposition upon thermolysis.†

The preparation of the secondary amine **24** was then completed by a sequence of reactions that commenced with the reduction of the lactam **20** with alane.

† In conjunction with these results, it is interesting to note that in early model studies, the related urethane **i** failed to undergo cyclization at temperatures up to about 300°.



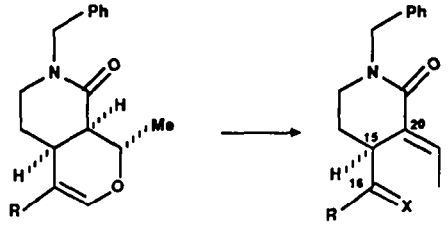
i

Subsequent installation of the requisite carbomethoxy function at C(16) of the resulting tertiary amine **22** was readily achieved in a two-step process[19] that was initiated with the acylation of the enol ether moiety with neat trichloroacetyl chloride to give an intermediate trichloroacetyl compound, which suffered a haloform-type cleavage upon heating in methanol in the presence of triethylamine to afford the vinylogous carbonate **23**. Finally, hydrogenolysis of the benzylic amino protecting group with Pearlman's catalyst then generated the bicyclic amine **24**, which was spectroscopically identical with material previously synthesized by Uskokovic. Inasmuch as **24** has been previously converted by sequential alkylation with tryptophyl bromide and several substituted tryptophyl bromides and oxidative cyclization into tetrahydroalstonine (**4**) and related heteroyohimbine alkaloids,[5d,i] its preparation in 18% overall yield by a linear sequence involving only 13 chemical operations constitutes in a formal sense the total syntheses of these natural products.

Having thus demonstrated that hetero-Diels–Alder reactions of α,β-unsaturated aldehydes could be exploited as a key step for the rapid construction of the fully intact D/E ring subunit of the heteroyohimbine alkaloids, there remained the crucial task of designing protocols for the refunctionalization of the *cis*-cycloadduct **20** to provide access to the D-ring subunit of those corynantheioid alkaloids that bear a C(20) *E*-ethylidene substituent.[20] Several preliminary experiments directed towards this objective with the model lactam **20** augur well for the successful application of these tactics to the total synthesis of geissoschizine (**6**) and related bases.

The elaboration of the C(20) *E*-ethylidene moiety has been addressed on two experimental fronts, the principal difference being the nature of the functionality on the alkyl appendage at C(15) in the 2-piperidone precursor of the D-ring. One relatively straightforward route to 4-alkyl-3(*E*)-ethylidene-2-piperidones was initiated with the acid-catalyzed methanolysis of the cycloadduct **20** to give a mixture ($\alpha:\beta \cong 4:1$) of the methyl glycosides **25** (Scheme 2). Subsequent treatment of **25** with 1,3-propanedithiol in the presence of boron trifluoride etherate gave the secondary alcohol **26** in which the aldehyde function is protected as a 1,3-dithiane. Base-induced β-elimination of the mesylate derived from **26** afforded the 3(*E*)-ethylidene piperidone **27** as the only product.

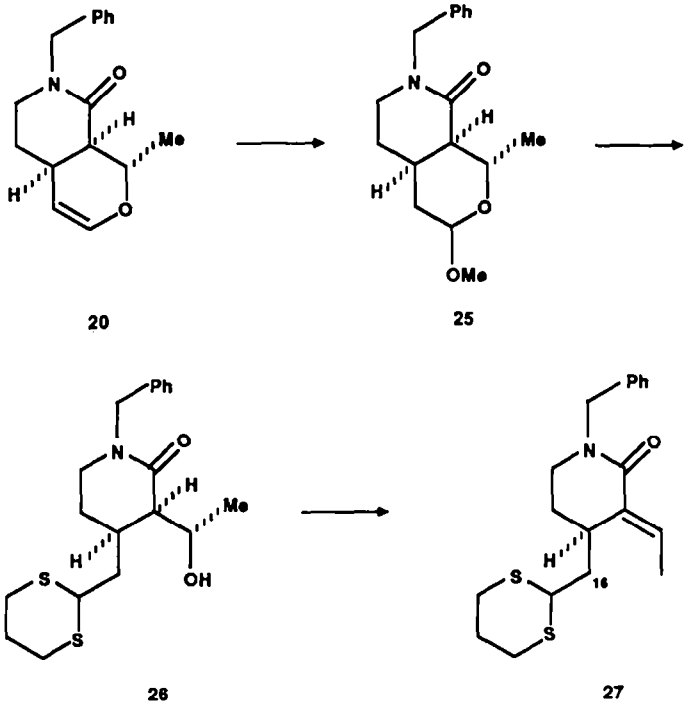
A more expeditious solution to the problem at hand would involve the direct deprotonation of either the *cis*-lactam **20** or **28** followed by scission of the dihydropyran ring via β-elimination of the ring oxygen atom to yield the corresponding unsaturated 2-piperidones **29** or **30**. That this strategy is not only



20: R = H
28: R = CO_2Me

29: R = CHO; X = H_2
30: R = CO_2Me; X = CHOH

appealing but also meritorious has been convincingly demonstrated in preliminary experiments in which treatment of the *cis*-cycloadduct **20** with excess sodium amide afforded the unsaturated 2-piperidone **29**. Efforts directed towards the extension of these tactics

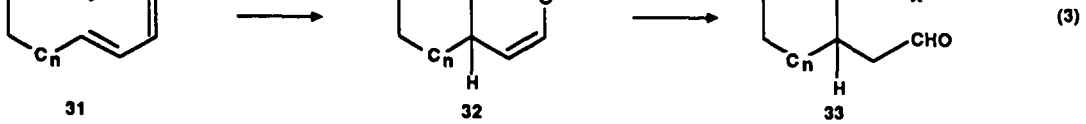


Scheme 2.

to the preparation of **30**, which possesses the precise functional array at C(15) and C(20) present in geissoschizine (**6**), are in progress.

CONCLUSION

Thus, the intramolecular Diels–Alder reactions of nitrogen-linked trienes in which the dienic partner is an α,β-unsaturated aldehyde can be exploited for the design of a facile entry to the D/E ring subunit of the heteroyohimboid alkaloids and the D-ring subunit of the corynantheioid alkaloids, as evidenced by the successful utilization of one such reaction in a novel synthesis of tetrahydroalstonine (**4**) and for the preparation of potential precursors of geissoschizine (**6**). Significantly, the basic strategy employed herein may be readily modified to accommodate the syntheses of related alkaloids such as ajmalicine (**5**), and the tactics outlined for the elaboration of the *E*-ethylidene substituent at C(20) should impact favorably upon the syntheses of geissoschizine (**6**) as well as the more complex alkaloids of the *Strychnos* family. Finally, it is noted that the intramolecular hetero-Diels–Alder reaction of α,β-unsaturated aldehydes should prove applicable to other areas of synthesis since ready access to fused dihydropyrans of the general type **32** is thereby provided (Eq. 3). Such substances would serve as useful intermediates in the synthesis of iridoid monoterpenes or 1,2-disubstituted cycloalkanes such as **33** in which the relative stereochemistry of the two alkyl appendages is secured in the cycloaddition step. These issues constitute the basis of current investigations in our laboratory, the results of which will be recorded in due course.



31 **32** **33** (3)

n = 1,2
X = H, OR, SR, NR_2

EXPERIMENTAL

General. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. M.ps were determined on a Thomas–Hoover capillary m.p. apparatus and are uncorrected. Ether, tetrahydrofuran (THF) and xylenes were distilled from either NaK or potassium/benzophenone ketyl immediately prior to use, and dimethyl sulfoxide (DMSO) and Et_3N were distilled from CaH_2. All reactions were executed under dry N_2 or Ar using oven-dried glassware. IR spectra were obtained as thin films (NaCl plates) or as solns in CH_2Cl_2 unless otherwise indicated. The ^{1}H-NMR spectra were determined at the indicated field as solns in $CDCl_3$ unless otherwise noted. Chemical shifts are expressed in ppm (δ-units) downfield from internal TMS. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; comp, complex multiplet; br, broad. Coupling constants are given in hertz (Hz). The ^{13}C-NMR spectra were determined at 20 MHz as solns in $CDCl_3$ unless otherwise indicated, and the chemical shifts are reported in ppm downfield from internal TMS.

3-Methoxymethyloxy-1-propyn-3-ol (**15**). Bromomethyl-methyl ether (59.1 g, 0.47 mol) was added dropwise with stirring to a soln of freshly distilled propargyl alcohol (25.0 ml, 0.43 mol) and distilled diethyl aniline (82.0 ml, 0.51 mol) in anhyd CH_2Cl_2 (125 ml) at −78°. The soln was warmed slowly to room temp and stirred for an additional 5 h, whereupon the crude mixture was cooled to 0° and diluted with Et_2O (125 ml). The resulting soln was washed with H_2O (3 × 100 ml), and the combined washings were extracted with Et_2O (2 × 100 ml). The combined organic layers were dried ($MgSO_4$), and the excess solvents were removed by fractional distillation. The crude product thus obtained was distilled to give **15** (41.3 g, 96%) as a colorless oil: b.p. 116–118° (760 mm Hg); IR ν 3330 cm^{-1}; ^{1}H-NMR (90 MHz) δ 4.60 (s, 2H), 4.11 (d, J = 2.5 Hz, 2H), 3.31 (s, 3H), 2.33 (t, J = 2.5 Hz, 1H); ^{13}C-NMR δ 94.8, 79.5, 74.4, 55.5, 54.0; mass spectrum, *m/z* 100.0521 ($C_5H_8O_2$ requires 100.0524) 100, 99, 69, 61, 55, 45, 39 (base), 29.

1-Methoxymethyloxy-2-pentyn-5-ol. To a soln of **15** (30.0 g, 0.30 mol) in THF (400 ml) at −78° was added slowly a soln of n-BuLi (2.75 M in hexane, 0.33 mol). After 30 min, ethylene oxide (52.0 g, 1.20 mol) was added, and the flask was tightly sealed. The mixture was warmed slowly to room temp and stirred at room temp for 20 h. The mixture was then partitioned between Et_2O (300 ml) and H_2O (150 ml), and the layers were separated. The organic layer was washed with brine (75 ml), dried ($MgSO_4$), concentrated under reduced pressure, and the crude product was purified by distillation to give 1-methoxymethyloxy-2-pentyn-5-ol as a colorless oil (35.1 g, 81%): b.p. 144–146° (40 mm Hg); ^{1}H-NMR (90 MHz) δ 4.61 (s, 2H), 4.10 (t, J = 2.5 Hz, 2H), 3.90–3.45 (comp, 3H), 3.32 (s, 3H), 2.57–2.27 (m, 2H); ^{13}C-NMR δ 94.8, 83.9, 77.0, 60.9, 55.5, 54.8, 23.1; mass spectrum, *m/z* 144.0781 ($C_7H_{12}O_3$ requires 144.0786), 127, 113, 99, 97, 83, 69, 55 (base), 45.

1-Methoxymethyloxypent-2(Z)-ene-5-ol (**16**). A soln of 1-methoxymethyloxy-2-pentyn-5-ol (25.0 g, 0.17 mol) in EtOAc (200 ml) containing Lindlar catalyst (5% Pd/$CaCO_3$/PbO) (0.50 g) was hydrogenated at 45 psi for 15 min. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation at 90–100° (bath temp) (0.15 mm Hg) to afford **16** (24.3 g, 96%) as a colorless oil: ^{1}H-NMR (90 MHz) δ 5.78–5.62 (m, 2H), 4.51 (s, 2H), 4.04 (br d, J = 5 Hz, 2H), 3.53 (br t, J = 6 Hz, 2H), 3.35 (s, 3H), 3.10 (br s, 1H), 2.33 (br q, J = 6 Hz, 2H); ^{13}C-NMR δ 130.3, 127.9, 95.5, 62.8, 61.7, 55.1, 31.2; mass spectrum, *m/z* 146.0940 ($C_7H_{14}O_3$ requires 146.0943) 146, 99, 45 (base).

1-Methoxymethyloxypent-2(Z)-enyl-5-p-toluenesulfonate. To a soln of **16** (10.0 g, 68.5 mmol) in CH_2Cl_2 (50 ml) at 0° was added in one portion a soln of *p*-toluenesulfonyl chloride (17.0 g, 89.1 mmol) in CH_2Cl_2 (25 ml) containing dry pyridine (8.1 g, 103 mmol). After storing at −15° for 12 h, the mixture was partitioned between Et_2O (150 ml) and H_2O (100 ml). The organic layer was extracted with ice-cold 1 N HCl (3 × 100 ml), H_2O (1 × 100 ml), and sat $NaHCO_3$ (2 × 100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by preparative HPLC (Porasil A; hexanes–EtOAc, 2:1) afforded 24.1 g (90%) of tosylate as a colorless oil: ^{1}H-NMR (90 MHz) δ 7.70 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 5.66–5.16 (m, 2H), 4.36 (s, 2H), 3.97 (m, 4H), 3.28 (s, 3H), 2.43 (s, 3H), 2.39 (m, 2H); ^{13}C-NMR δ 144.8, 133.3, 130.0, 129.5, 127.9, 127.0, 95.6, 69.4, 62.6, 55.2, 27.4, 21.6; mass spectrum, *m/z* 300.1040 ($C_{14}H_{20}SO_5$ requires 300.1031) 171, 129, 84, 45 (base).

N-Benzyl-1-methoxymethyloxypent-2(Z)-ene-5-amine (**17**). A soln containing freshly distilled benzylamine (8.6 g, 80.0 mmol), 1-methoxymethyloxypent-2(*Z*)-enyl-5-*p*-toluenesulfonate (12.0 g, 40.0 mmol) and NaI (0.25 g) in dry DMSO (50 ml) was stirred at room temp for 20 h, whereupon the reaction was quenched by the addition of cold 1% NaOH (160 ml). The aq mixture was extracted with Et_2O (3 × 100 ml), and the combined organic layers were washed with H_2O (1 × 100 ml) and sat brine (1 × 100 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (neutral alumina, 80 g; hexanes–EtOAc, 5 : 1) to provide **17** (8.33 g, 88%) as a pale yellow oil : b.p. 130° (0.02 mm Hg); ^{1}H-NMR (90 MHz) δ 7.17 (comp, 5H), 5.71–5.31 (m, 2H), 4.46 (s, 2H), 4.03 (br d, J = 5 Hz 2H), 3.67 (s, 2H), 3.23 (s, 3H), 2.73–2.48 (m, 2H), 2.39–2.07 (m, 2H), 1.35 (br s, 1H); ^{13}C-NMR δ 140.1, 131.0, 128.0, 127.7, 127.1, 126.5, 95.3, 62.5, 54.8, 53.5, 48.4, 27.9; mass spectrum, *m/z* 235.1575 ($C_{14}H_{21}NO_2$ requires 235.1572), 190, 173, 120 (base), 91, 65.

N-Benzyl-N-[1-methoxymethyloxypent-2(Z)-en-5-yl]-crotonamide (**18**). To a stirred soln of crotonic acid (0.44 g, 5.2 mmol) in dry CH_2Cl_2 (10 ml) containing Et_3N (1.59 g, 10.8 mmol) at −15° was added ethyl chloroformate (0.61 g, 5.7 mmol), and the stirring was continued for 30 min at −15°. The soln was cooled to −78°, and a soln of **17** (1.23 g, 5.2 mmol) in CH_2Cl_2 (20 ml) was added slowly. The bath was allowed to warm slowly to room temp and was stirred at room temp for 6.5 h. Et_2O (50 ml) and H_2O (50 ml) were added and the layers separated. The organic layer was washed with sat $NaHCO_3$aq (20 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by HPLC (Porasil A; hexanes–EtOAc, 1 : 1) to give **18** (1.33 g, 85%) as a pale yellow oil : IR ν 1660, 1620 cm^{-1}; ^{1}H-NMR (90 MHz) δ 7.25 (br s, 5H), 7.00 (br dq, J = 21, 6 Hz, 1H), 6.42–6.05 (m, 1H), 5.60 (br d, J = 9 Hz, 1H), 5.54 (br d, J = 9 Hz, 1H), 4.60 (br s, 4H), 4.05 (br d, J = 5 Hz, 2H), 3.55–3.05 (m, 2H), 3.35 (s, 3H), 2.50–2.15 (m, 2H), 2.00–1.72 (m, 3H); ^{13}C-NMR δ 165.9, 141.4, 128.5, 128.1, 127.2, 122.0, 95.2, 62.3, 54.8, 46.3, 17.9; mass spectrum, *m/z* 303.1841 ($C_{18}H_{25}NO_3$ requires 303.1834), 242, 188 (base), 120, 106, 91, 69.

N-Benzyl-N-[1-hydroxypent-2(Z)-en-5-yl]-crotonamide (**19**). A soln of **18** (315 mg, 1.04 mmol) in EtOH (10 ml) containing conc H_2SO_4 (0.03 ml) was heated at reflux for 9 h, whereupon the solvent was removed under reduced pressure. Et_2O (10 ml) and sat $NaHCO_3$aq were added to the residue, and the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **19** (257 mg, 95%) as a pale yellow, viscous oil : IR ν 1660, 1610 cm^{-1}; ^{1}H-NMR (90 MHz) δ 7.25 (br s, 5H), 7.00 (dq, J = 21, 7 Hz, 1H), 6.50–6.00 (m, 1H), 5.90–5.20 (m, 2H), 4.60 (br s, 2H), 4.10 (br d, J = 6 Hz, 2H), 3.90 (br s, 1H), 3.53–3.10 (m, 2H), 2.30 (br q, J = 7 Hz, 2H), 2.03–1.60 (m, 3H); ^{13}C-NMR δ 166.9, 142.5, 128.8, 128.0, 127.8, 127.5, 126.5, 121.7, 57.9, 46.7, 18.2; mass spectrum, *m/z* 259.1576 ($C_{16}H_{21}NO_2$ requires 259.1572), 188 (base), 120, 106, 91, 69.

N-Benzyl-N-[pent-2(E)-enal-5-yl]-crotonamide (**11**). To a soln of oxalyl chloride (500 mg, 4.97 mmol) in CH_2Cl_2 (5.0 ml) under dry N_2 at −78° was added DMSO (750 mg, 9.8 mmol), and the resulting soln was stirred at −78° for 30 min. A soln of **19** (300 mg, 1.14 mmol) in CH_2Cl_2 (3.5 ml) was added slowly dropwise, and stirring was continued at −78° for 1 h, at which point Et_3N (2.0 g, 20.2 mmol) was added. The cooling bath was removed, and the reaction was allowed to proceed at room temp for 15 min, whereupon CH_2Cl_2 (20 ml) was added. The resulting soln was then heated at reflux for 11 h. After cooling, H_2O (30 ml) and Et_2O (60 ml) were added, and the layers were separated. The aq layer was washed with Et_2O (60 ml), and the combined organic layers were washed with sat brine (30 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel, 10 g; hexanes–EtOAc, 1 : 3) afforded **11** (231 mg, 79%) as a pale gold, viscous oil : IR ν 1690, 1660, 1610 cm^{-1}; ^{1}H-NMR (200 MHz) δ 9.46 (d, J = 8.0 Hz, 1H), 7.45–7.11 (m, 5H), 7.00 (dq, J = 15.0, 7.5 Hz, 1H), 6.78 (dt, J = 16.0, 7.0 Hz, 1H), 6.25 (br d, J = 15.0 Hz, 1H), 6.07 (dd, J = 16.0, 8.0 Hz, 1H), 4.60 (br s, 2H), 3.55 (br t, J = 7.0 Hz, 2H), 2.55 (q, J = 7.0 Hz, 2H), 1.85 (br d, J = 7.5 Hz, 3H); ^{13}C-NMR δ 193.4, 166.9, 142.9, 134.3, 128.9, 127.8, 126.6, 121.5, 45.2, 18.2; mass spectrum, *m/z* 257.1405 ($C_{16}H_{19}NO_2$ requires 257.1416), 188, 160, 120, 106, 91, 69 (base), 41.

(1*S**, 4a*R**, 8a*R**) - 7 - *Benzyl* - 1 - *methyl* - 4a,5,6,8a - *tetrahydro* - 1H - *pyrano*[3,4 - *c*]*pyridin* - 8(7H) - *one* (**20**). A soln of **11** (500 mg, 1.95 mmol) in degassed xylenes (100 ml) in a resealable glass bomb was heated at 190° for 18 h. Removal of the solvent under reduced pressure gave a mixture of *cis* and *trans* fused lactams **20** and **21** (*ca* 5 : 1 ratio) which was purified by HPLC (Porasil A; hexanes–EtOAc, 2 : 1) to give **20** (365 mg, 73%) as a pale gold, viscous oil and **21**. For **20**: IR ν 1660, 1640 cm^{-1}; ^{1}H-NMR (200 MHz) δ 7.40–7.17 (m, 5H), 6.42 (dd, J = 6.5, 2.0 Hz, 1H), 4.95 (dq, J = 4.0, 7.5 Hz, 1H), 4.68 (d, J = 15.0 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.49 (m, 1H), 3.27 (ddd, J = 4.5, 10.0, 11.5 Hz, 1H), 3.07 (dt, J = 11.5, 4.5 Hz, 1H), 2.82–2.68 (m, 1H), 2.48 (dd, J = 7.0, 4.0 Hz, 1H), 2.07–1.69 (m, 2H), 1.37 (d, J = 7.5 Hz, 3H); ^{13}C-NMR δ 169.0, 144.4, 137.2, 128.5, 127.8, 127.2, 100.6, 70.4, 50.7, 44.7, 44.0, 27.0, 25.7, 18.2; mass spectrum, *m/z* 257.1421 ($C_{16}H_{19}NO_2$ requires 257.1416), 242, 91 (base).

(1*S**, 4a*S**, 8a*R**) - 7 - *Benzyl* - 4a,5,6,7,8,8a - *hexahydro* - 1 - *methyl* - 1H - *pyrano*[3,4 - *c*]*pyridine* (**22**). To a soln of freshly prepared AlH_3 (8.25 mmol) in THF (15 ml) was added **20** (120 mg, 0.5 mmol) in dry THF (3 ml), and the soln was stirred at room temp for 1 h. The reaction was quenched by the slow addition of 50% THF aq (3 ml). The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with Et_2O (2 × 25 ml), and the combined extracts were dried (Na_2SO_4) and concentrated to afford **22** (103 mg, 90%) as a pale gold, viscous oil : IR ν 1660 cm^{-1}; ^{1}H-NMR (360 MHz) δ 7.26 (m, 5H), 6.25 (dd, J = 6.0, 1.5 Hz, 1H), 4.57 (dd, J = 5.0, 6.0 Hz, 1H), 4.15 (p, J = 6.5 Hz, 1H), 3.50 (d, J = 13.0 Hz, 1H), 3.33 (d, J = 13.0 Hz, 1H), 2.63–2.45 (m, 2H), 2.32–2.20 (m, 3H), 1.84–1.58 (comp, 3H), 1.14 (d, J = 6.5 Hz, 3H); ^{13}C-NMR δ 142.5, 138.6, 129.1, 128.2, 127.0, 103.9, 71.3, 63.5, 54.0, 52.6, 38.5, 31.3, 28.2, 18.5; mass spectrum, *m/z* 243.1628 ($C_{16}H_{21}NO$ requires 243.1623), 200, 172, 91 (base).

Methyl (1*S**, 4a*S**, 8a*R**) - 7 - *benzyl* - 4a,5,6,7,8,8a - *hexahydro* - 1 - *methyl* - 1H - *pyrano*[3,4 - *c*]*pyridine* - 4 - *carboxylate* (**23**). A mixture of **22** (70 mg, 0.29 mmol) and trichloroacetyl chloride (0.7 ml, 6.3 mmol) was heated at 68° for 2.5 h. The soln was diluted with Et_2O (10 ml) and cooled, and the resulting mixture was basified with conc NaOH. The layers were separated, and the organic layer was washed with sat $NaHCO_3$aq (3 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was eluted through a column of basic alumina (300 mg) with a mixture of hexanes and EtOAc (3 : 1). After evaporation of the eluents the intermediate trichloroketone was dissolved in MeOH (1.5 ml) containing Et_3N (145 mg, 1.4 mmol), and the soln was heated with stirring at 56° for 1.5 h. The excess solvent was removed under reduced pressure, Et_2O (10 ml) added, and the organic phase was washed with sat $NaHCO_3$ aq (3 ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave **23** (71 mg, 81%) as a gold, viscous oil : IR ν 1700, 1630 cm^{-1}; ^{1}H-NMR (360 MHz) δ 7.51 (s, 1H), 7.28 (m, 5H), 4.49 (dq, J = 10.0, 6.0 Hz, 1H), 3.69 (s, 3H), 3.55 (d, J = 13.0 Hz, 1H), 3.23 (d, J = 13.0 Hz, 1H), 2.85 (br d, J = 12.0 Hz, 2H), 2.47 (dt, J = 12.0, 4.5 Hz, 1H), 2.17–1.97 (m, 3H), 1.65–1.50 (m, 2H), 1.13 (d, J = 6.0 Hz, 3H); ^{13}C-NMR δ 167.9, 155.1, 138.9, 128.9, 128.2, 127.1, 110.3, 72.4, 63.4, 54.5, 53.9, 50.9, 38.5, 30.8, 30.3, 18.3; mass spectrum, *m/z* 301.1687 ($C_{18}H_{23}NO_3$ requires 301.1678), 172, 146, 120, 91 (base).

Methyl (1*S**, 4a*S**, 8a*R**) - 4a,5,6,7,8,8a - *hexahydro* - 1 - *methyl* - 1H - *pyrano*[3,4 - *c*]*pyridine* - 4 - *carboxylate* (**24**). A soln of **23** (79 mg, 0.26 mmol) in glacial AcOH (0.6 ml) containing 20% $Pd(OH)_2$/C (31 mg) was stirred under H_2 (1.1 atm) for 4.5 h. The mixture was filtered, the filtrate was concentrated under reduced pressure, and CH_2Cl_2 (25 ml) was added. The resulting soln was washed with a minimal amount of sat K_2CO_3aq and dried (Na_2SO_4), and the solvent was

removed under reduced pressure to give **24** (49 mg, 90%) as a gold, viscous oil: IR ν 1700, 1630 cm^{-1}; ^{1}H-NMR (200 MHz) δ 7.52 (s, 1H), 4.52 (dq, J = 10.5, 6.5 Hz, 1H), 3.70 (s, 3H), 3.22 (br d, J = 12.5 Hz, 1H), 3.04 (br d, J = 11.5 Hz, 1H), 2.95 (dd, J = 12.5, 4.0 Hz, 1H), 2.72 (dt, J = 3.0, 12.0 Hz, 1H), 2.58 (dt, J = 11.5, 5.0 Hz, 1H), 2.00 (m, 1H), 1.69 (br s, 1H), 1.53 (m, 2H), 1.38 (d, J = 6.5 Hz, 3H); ^{13}C-NMR δ 167.7, 155.1, 110.1, 71.7, 50.9, 46.9, 46.3, 37.7, 30.8, 29.8, 18.5; mass spectrum, *m/z* 211.1213 ($C_{11}H_{17}NO_3$ requires 211.1208), 180, 150, 110, 57 (base).

Mixture of (1*R**, 3*R** *and* 3*S**, 4a*S**, 8a*R**) - 7 - *benzyl* - 3,4,4a,5,6,8a - *hexahydro* - 3 - *methoxy* - 1 - *methyl* - 1H - *pyrano*[3,4 - *c*]*pyridin* - 8(7H) - *ones* (**25**) *from* **20**. A soln of **20** (273 mg, 1.06 mmol) in MeOH (13 ml) containing 70% perchloric acid (5 drops) was stirred at room temp for 15 h and then concentrated to approximately 3 ml under reduced pressure. The residue was dissolved in sat $NaHCO_3$ (40 ml), and the aq soln was extracted with CH_2Cl_2 (3 × 50 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was eluted from a silica column (8 g) with hexanes–EtOAc (1 : 1) to afford a mixture (4 : 1) of the anomers **25** as a pale yellow oil (292 mg, 95%): IR ν 1640, 1500 cm^{-1}; ^{1}H-NMR (360 MHz) δ 1.44 (d, J = 6.5 Hz, 3H), 1.57 (m, 1H), 1.70 (m, 1H), 1.87 (dt, J = 4.5, 4.5 Hz, 1H), 2.19 (m, 1H), 2.43 (m, 1H), 3.15 (m, 3H), 3.32 (s, 3H), 4.12 (dq, J = 6.5, 6.5 Hz, 1H), 4.47 (d, J = 14.5 Hz, 1H), 4.62 (d, J = 14.5 Hz, 1H), 4.70 (dd, J = 3.5, 3.5 Hz, 1H), 7.27 (m, 5H); ^{13}C-NMR δ 169.3, 137.1, 128.3, 127.7, 127.1, 98.0, 63.0, 54.6, 50.0, 48.0, 45.8, 32.4, 29.9, 28.7, 20.5; mass spectrum, *m/z* 289.1685 ($C_{17}H_{23}NO_3$ requires 289.1678), 274, 257, 188, 91 (base).

(1*R**, 3*R**, 4*R**) - N - *Benzyl* - 3 - [1′(*S**) - *hydroxyethyl*] - 4 - [2-(1″,3″ - *dithioano*)*ethyl*]*piperidine* - 2 - *one* (**26**). BF_3 etherate (8 drops) was added to an ice-cooled soln of **25** (205 mg, 0.72 mmol) and 1,3-propanedithiol (157 mg, 1.46 mmol) in CH_2Cl_2 (40 ml), and the mixture was stirred at room temp for 4.5 h. The resulting soln was poured into 2 N NaOH (100 ml), and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by column chromatography (silica gel, 6 g; hexanes–EtOAc, 1 : 1) to afford **26** (258 mg, 97%) as a pale yellow, viscous oil: IR ν 3420, 1640 cm^{-1}; ^{1}H-NMR (360 MHz) δ 1.28 (d, J = 6.5 Hz, 3H), 1.65 (ddd, J = 15.0, 9.0, 6.0 Hz, 1H), 1.81 (m, 3H), 2.12 (m, 1H), 2.23 (ddd, J = 14.5, 9.0 6.0 Hz, 1H), 2.57 (m, 1H), 2.67 (dd, J = 5.5, 4.0 Hz, 1H), 2.83 (m, 4H), 3.25 (dt, J = 6.5, 6.5 Hz, 2H), 4.02 (br s, 1H), 4.07 (dd, J = 9.0, 6.0 Hz, 1H), 4.35 (br m, 1H), 4.56 (d, J = 14.5 Hz, 1H), 4.64 (d, J = 14.5 Hz, 1H), 7.29 (m, 5H); ^{13}C-NMR δ 171.3, 136.8, 128.6, 128.1, 127.5, 65.9, 50.3, 50.1, 44.7, 44.6, 35.1, 30.1, 29.9, 25.9, 25.7, 20.7; mass spectrum, *m/z* 365.1472 ($C_{19}H_{27}NO_2S_2$ requires 365.1483), 347, 321, 288, 215, 91 (base).

(4*R**) - N - *Benzyl* - 3 - (*E*) - *ethylideno* - 4 - [2 - (1′,3′ - *dithiano*)*ethyl*]*piperidine* - 2 - *one* (**27**). Methanesulfonyl chloride (142 mg, 1.24 mmol) was added with stirring to an ice-cooled soln of **26** (151 mg, 0.41 mmol) and Et_3N (209 mg, 2.07 mmol) in CH_2Cl_2 (8 ml), and the resulting soln was stirred at room temp for 16 h at which time it was poured into 2 N HCl (75 ml). The mixture was extracted with CH_2Cl_2 (3 × 60 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude mesylate (168 mg, 0.38 mmol) thus obtained was dissolved in MeOH (8 ml) containing NaOMe (61 mg, 1.14 mmol) and heated under reflux for 1.5 h. The excess solvent was then removed under reduced pressure and H_2O (70 ml) added. The mixture was extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel, 6 g; hexanes–EtOAc, 2 : 1) afforded **27** (125 mg, 95%) as a pale yellow, viscous oil: IR ν 1670, 1630 cm^{-1}; ^{1}H-NMR (360 MHz) δ 1.81 (m, 3H), 1.87 (d, J = 7.0 Hz, 3H), 1.94 (m, 2H), 2.33 (dt, J = 3.5, 3.5 Hz, 1H), 2.84 (m, 4H), 3.17 (m, 1H), 3.32 (m, 1H), 3.38 (dt, J = 12.5, 12.5 Hz, 1H), 3.91 (t, J = 7.0 Hz, 1H), 4.52 (d, J = 14.5 Hz, 1H), 4.76 (d, J = 14.5 Hz, 1H), 7.02 (q, J = 7.0 Hz, 1H), 7.28 (5H, m); ^{13}C-NMR δ 164.3, 137.1, 134.5, 132.8, 128.3, 127.6, 127.0, 50.5, 44.5, 42.5, 37.2, 30.1, 29.5, 25.6, 13.5; mass spectrum, *m/z* 347.1383 ($C_{19}H_{25}NOS_2$ requires 347.1377), 257, 215, 91 (base).

(4*R**) - N - *Benzyl* - 3 - (*E*) - *ethylideno* - 4 - (2 - *oxo* - *ethyl*)*piperidine* - 2 - *one* (**29**). To a suspension of $NaNH_2$ (300 mg, 7.7 mmol) in THF (15 ml) under N_2 was added **20** (150 mg, 0.58 mmol), and the resulting mixture was stirred at room temp until **20** could no longer be detected by GLC chromatography. The mixture was then cooled to 0°, and H_2O (10 ml) and Et_2O (20 ml) were added and the layers separated. The organic layer was dried (Na_2SO_4) and filtered, and the excess solvent was removed under reduced pressure. The crude product was purified by column chromatography (basic Al_2O_3), using EtOAc as eluent, to give **29** (90 mg, 60%) as a colorless oil: IR ν 1735, 1660, 1620 cm^{-1}; ^{1}H-NMR (360 MHz) δ 9.76 (s, 1H), 7.35–7.25 (m, 5H), 7.02 (q, J = 7.3 Hz, 1H), 4.74 (d, J = 14.5 Hz, 1H), 4.59 (d, J = 14.5 Hz, 1H), 3.53 (m, 1H), 3.35 (dt, J = 4.4, 12.6 Hz, 1H), 3.19 (ddd, J = 12.8, 5.8, 2.2 Hz, 1H), 2.57 (ddd, J = 17.1, 8.9, 2.1 Hz, 1H), 2.47 (dd, J = 17.1, 5.8 Hz, 1H), 2.00–1.94 (m, 1H), 1.86–1.81 (m, 1H), 1.81 (d, J = 7.3 Hz, 3H); ^{13}C-NMR δ 200.3, 164.3, 137.3, 134.4, 132.4, 128.6, 128.0, 127.4, 50.9, 45.6, 42.6, 27.6, 26.0, 13.6; mass spectrum, *m/z* 257.1421 ($C_{16}H_{19}NO_2$ requires 257.1416), 229, 214, 91 (base).

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