AN APPROACH TO OPEN CHAIN AND MODIFIED HETEROCYCLIC ANALOGUES OF THE ACETYLCHOLINESTERASE INHIBITOR, HUPERZINE A, THROUGH A BICYCLO[3.3.1]NONANE INTERMEDIATE

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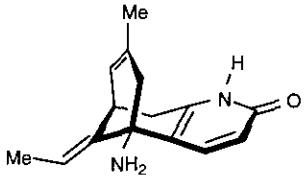
Abstract - The use of the bicyclo[3.3.1]nonane derived keto urethane (**3**) in a general synthesis of open chain and modified heterocyclic analogues of huperzine A was investigated and resulted in the preparation of the dimethylcarbamoyloxy analogue (**27**). Thiazole annulation by the Gewald procedure gave only the undesired regioisomer (**36**).

Huperzine A (**1**), an alkaloid isolated from the clubmoss *Huperzia serrata* (Thunb) Trev. = *Lycopodium serratum* Thunb. which has long been used as a Chinese folk medicine[1] holds considerable promise in the treatment of Alzheimer's disease due to its acetylcholinesterase inhibition.[2] The scarcity of huperzine A from natural sources has induced us[3] and others[4] to develop total syntheses, and the desire to uncover structure-activity relationships in order to improve upon the natural product has spurred the preparation of numerous analogues,[3,5,6] so far to no avail. Work in our group has centered around the dihydroquinoline intermediate (**2**) onto which appropriate C_3 bridges were grafted using a one-pot Michael addition-aldol condensation protocol. The disadvantage of this approach resides in the obvious fact that each type of heterocyclic ring system that is to replace the pyridone ring, or functional group patterns not containing a ring at all (to obtain "open-chain" analogues) will require a whole new set of intermediates from early stages on. Whereas we have in the meantime embarked on several such undertakings[7] and found them not without difficulty, despite the apparent analogy to our original synthesis, the present paper describes the initial results and problems of a more ambitious strategy, namely to procure open-chain and modified heterocyclic huperzine A analogues using the functionalized bicyclo[3.3.1]nonane derivative (**3**) as a common intermediate.



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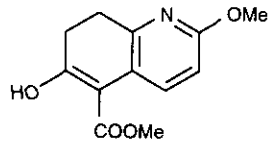

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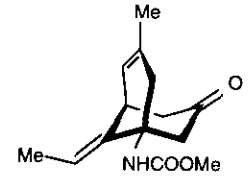

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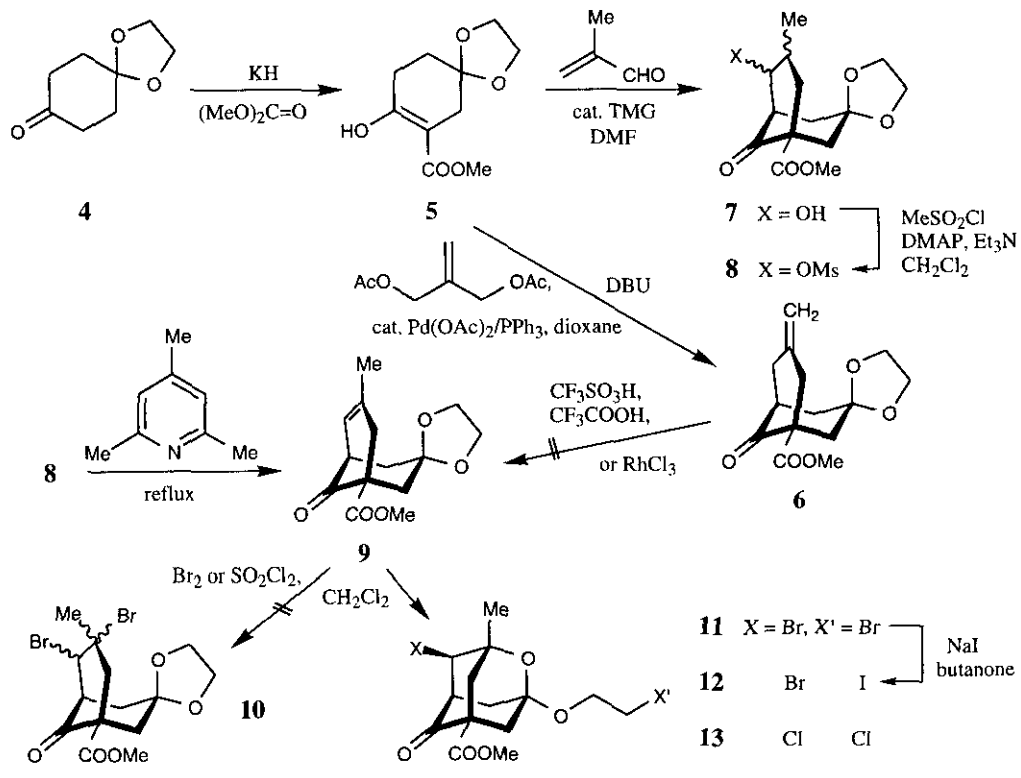
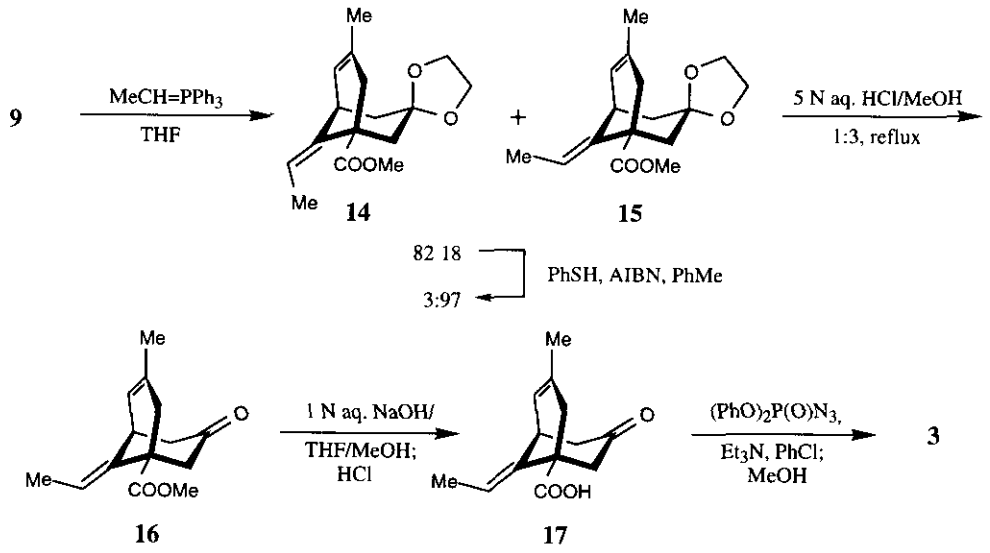
Preparation of the keto urethane (3). Cyclohexane-1,4-dione monoethylene ketal (**4**) served as a convenient starting material containing both a free carbonyl group for elaborating the bicyclic skeleton as well as introducing the ethylidene group, and a masked one to become, after deprotection, the ketone function of the target compound. While its methoxycarbonyl derivative (**5**) has been described in the literature,[8] we followed our dimethyl carbonate/KH protocol as in the preparation of **2** with good success. The resulting β-keto ester (**5**) smoothly underwent the Pd-catalyzed cycloalkylation[4] with 2-methylene-1,3-propanediol diacetate to afford the exocyclic olefin (**6**), but this compound failed to isomerize to the required intermediate (**9**) under acid or rhodium catalysis.[9] We therefore returned to our original Michael addition-aldol reaction sequence and obtained the bicyclic ketol (**7**) after a slight modification of the reaction conditions (methacrolein, cat. 1,1,3,3-tetramethylguanidine, DMF rather than CH_2Cl_2 as the solvent). The resulting mixture of stereoisomers was *directly mesylated* ($MeSO_2Cl$, cat. DMAP, CH_2Cl_2). Although the two major diastereoisomers of the mesylate (**8**) could be crystallized after careful column chromatography, it was more practical to subject the crude mixture directly to the elimination conditions (2,4,6-collidine, reflux).[10] In this manner, olefin (**9**) was obtained from **4** in a total yield of *25%, the lowest-yielding step being, as in similar cases, the elimination.* While **8** gave a correct combustion analysis after chromatography and distillation, both nmr and gc-ms pointed to the presence of minor impurities; according to gc-ms, these are isomers of **9**. Unfortunately, in contrast to the corresponding highly crystalline huperzine A intermediate, compound (**9**) is an oil. Uncertain whether later intermediates could be readily crystallized, we spent some effort to prepare a crystalline derivative from which pure **9** could be recovered, and first attempted the bromination of the C=C double bond (Br_2, CH_2Cl_2, -78 °C). A highly

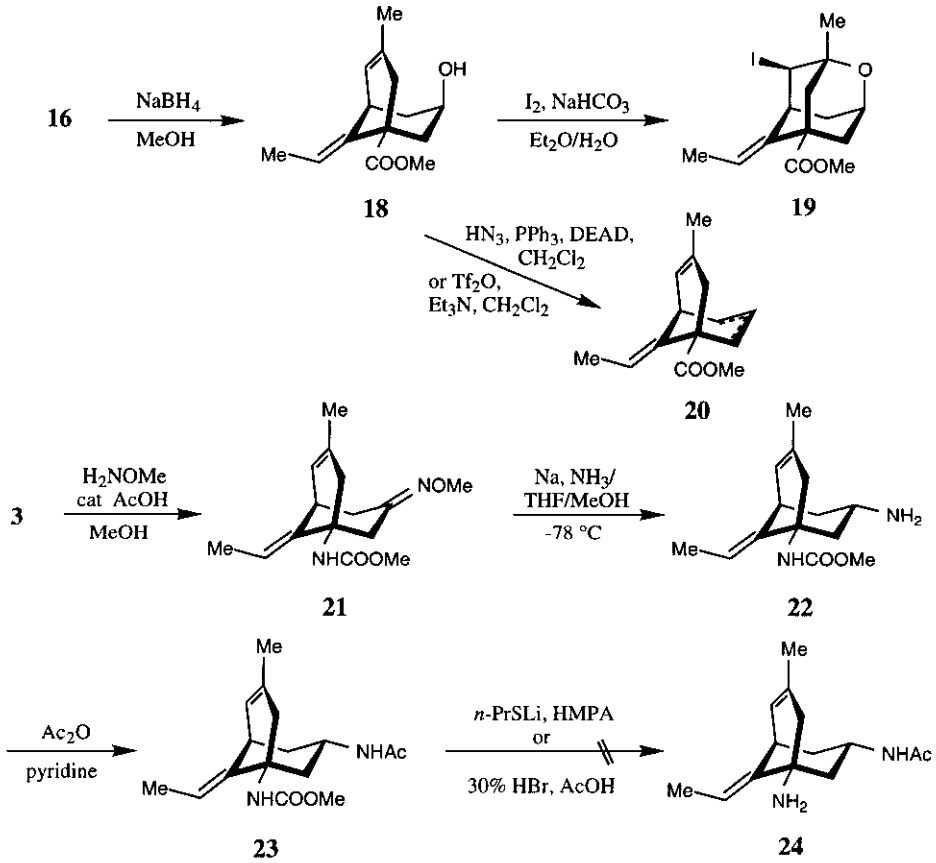




crystalline product was obtained in 69% yield which exhibited the correct molecular mass (gc-ms) but on treatment with NaI (butanone, 65 °C), rather than reverting to **9**, was transformed into a mixed bromide-iodide. The 135° DEPT ^{13}C nmr spectrum of this material exhibited the signal of the iodinated carbon atom as expected at high field (δ = 2.89) but also indicated that it was strongly coupled to two protons! This result was incompatible with the expected structure (**10**) for the initial dibromide but fitted nicely to the oxaadamantane (**11**) derived from the intermediate bromonium ion by neighboring group participation of the dioxolane ring, and its derived iodide (**12**). An analogous dichloride (**13**) was obtained from **9** with SO_2Cl_2. We briefly examined whether **11** could be used as an intermediate but obtained only traces of an olefination product on treatment with MeCH=PPh_3, presumably because **11** acted predominantly as an alkylating agent. Attempted removal of the reactive 2-bromoethoxy group by transketalization (MeOH, cat. camphorsulfonic acid, 60 °C) resulted only in the recovery of starting material. In a different approach, treatment of **9** with semicarbazide hydrochloride (NaOAc, isopropanol, reflux) produced two compounds in moderate yield neither of which was the expected semicarbazone.

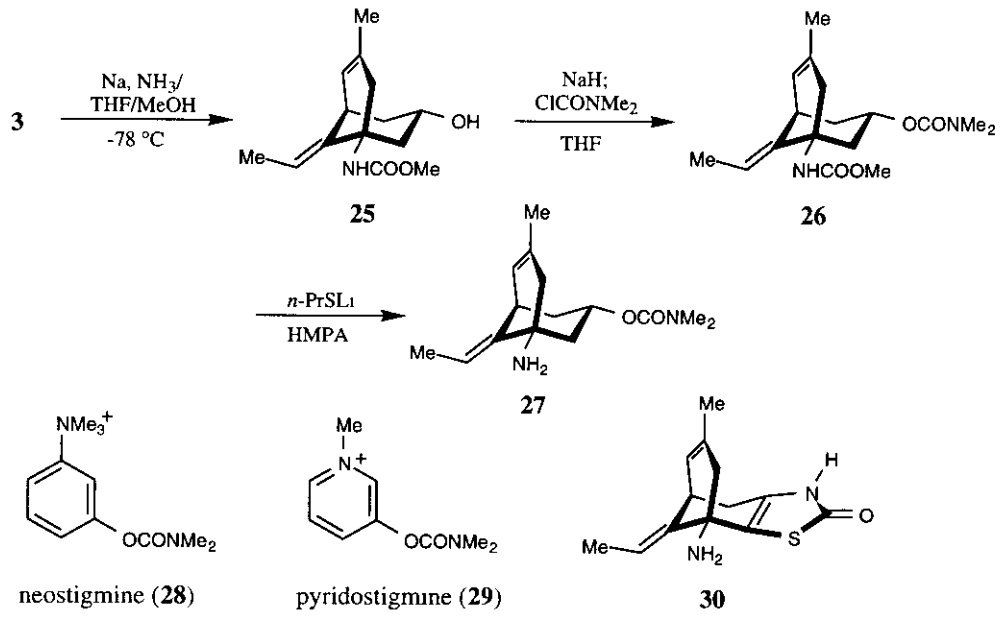
At this point, we returned to the main path of our synthesis. Olefination of **9** with MeCH=PPh_3 procured the *Z* olefin (**14**) in 82% diastereoselectivity which was subsequently isomerized to the *E* isomer (**15**) (97% stereochemical purity) with thiophenol and AIBN in toluene. Deketalization of this intermediate followed by saponification yielded the highly crystalline keto acid (**17**) which was pure by nmr spectroscopy and combustion analysis after a single crystallization. Curtius degradation ($(PhO)_2P(O)N_3$, Et_3N, PhCl; MeOH) of this acid uneventfully gave the keto urethane (**3**).

Attempted Synthesis of the Acetamido Analogue (24). This compound which maintains the hydrogen bonding capabilities of huperzine A and does not introduce steric bulk was designed to probe the importance of the rigidity and/or unsaturation of the pyridone ring to the biological activity of huperzine A. Our first approach began with the $NaBH_4$ reduction of keto ester (**16**) to the axial alcohol (**18**) which has the correct

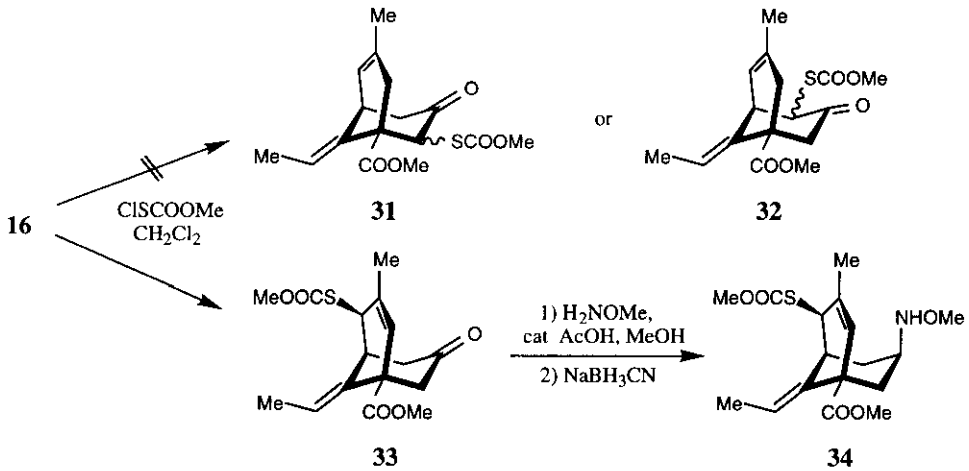


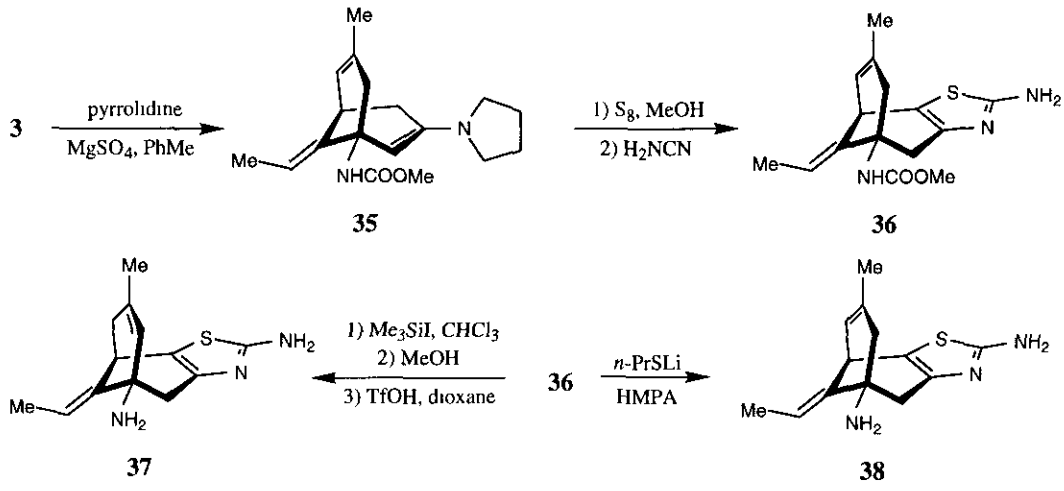
stereochemistry (confirmed by intramolecular iodoetherification to form the oxaadamantane (**19**)) for the introduction of an equatorial nitrogen atom by nucleophilic substitution. Unfortunately, both under Mitsunobu conditions and on *O*-sulfonylation, a regioisomeric olefin mixture (**20**) was obtained as the only identifiable product. In an alternative strategy, the keto urethane (**3**) was converted into its *O*-methyloxime (**21**) and thence by Na/NH_3 reduction to the equatorial amine (**22**). While *N*-acetylation uneventfully gave the amide (**23**), its deprotection (*n*-PrSLi, HMPA, 90 °C or 23 °C; 30% HBr/AcOH, 23 °C; or Me_3SiI, $CHCl_3$ with or without addition of Et_3N) resulted in intractable mixtures. The judicious choice of an *N*-protective group other than methoxycarbonyl may eventually overcome this difficulty.

Synthesis of the Dimethylcarbamoyloxy Analogue (27). This compound combines structural features of huperzine A with those of several other acetylcholinesterase inhibitors such as neostigmine (**28**) or pyridostigmine (**29**) which contain a dimethylcarbamoyloxy group. It was readily arrived at through Na/NH_3 reduction of **3** and carbamoylation of the resulting equatorial alcohol (**25**). Attempted deprotection with Me_3SiI resulted in decomposition; with *n*-PrSLi in HMPA, **27** was formed in 74% yield.



Investigations towards the Synthesis of the Thiazole Analogue (30). Iso-π-electronic replacement of one of the C=C double bonds in the pyridone ring of huperzine A by a sulfur atom leads to structure (**30**). We hoped to arrive at a suitable precursor by means of a recently described[11] thiazolinone annulation which proceeds through sulfenylation of a ketone with methoxycarbonylsulfenyl chloride, followed by cyclization with NH_4OAc in acetic acid. When applied to ketone (**16**), two regioisomeric intermediates (**31**) and/or (**32**) could be expected. In the event, a sulfenylation product was obtained in 46% yield which proved unexpectedly reluctant to undergo cyclization under the above-mentioned or a variety of modified conditions. In one attempt to find an alternative transformation, the derived *O*-methyloxime was reduced with $NaBH_3CN$ to yield a hydroxylamine the ^1H nmr spectrum of which, surprisingly, exhibited couplings of the proton in α position to the





hydroxylamine nitrogen with two adjacent methylene groups. The magnitude of these couplings from 5.5 to 6.5 Hz demonstrates axial orientation of the nitrogen. Together with the observation that the ethylidene group has remained intact, this indicates that the sulfenylation has taken place at the endocyclic olefin moiety. The absence of couplings between the corresponding olefinic proton as well as the proton in α position to the sulfur atom with the bridgehead proton argues in favor of a double bond position and substituent stereochemistry as depicted in formula (**34**). The initial sulfenylation product is therefore **33**, a compound evidently not suitable for thiazolinone annulation.

In a second approach, use was made of the Gewald aminothiazole synthesis[12] in which an enamine is sulfenylated with elemental sulfur and the resulting thiolate reacted with cyanamide. Starting from the keto urethane (**3**), a single aminothiazole (**36**) was obtained in 88% yield. To our disappointment, it possesses the wrong regiochemistry as evidenced by the absence of ^{1}H nmr coupling between the bridgehead proton and the benzylic methylene group. Examination of the crude enamine, on the other hand, revealed that the corresponding coupling constants for the major component (**35**) are in the usual range for the desired regioisomer, namely 1.5 and 4.5 Hz; furthermore, the enamine proton appears as a singlet at δ 4.17. The regioisomerization of enamines is not unusual[13] but occurs here under mild conditions during the sulfenylation; the desired regioisomer is the less reactive one for steric reasons. Deprotection of **36** with Me_3SiI gave us another surprise: In place of the expected product (**38**), mostly its isomer (**37**) with a shifted endocyclic double bond was formed. The rearrangement was driven to completion by subsequent treatment with triflic acid in dioxane.[5] Since no such isomerization is observed in the synthesis of huperzine A, but does occur in another case similar to the one described here,[7] and since **37** has the same relative position of the endocyclic double bond and the condensed aromatic ring as these examples, we conclude that this arrangement of the unsaturation is the thermodynamically more stable one. It should be possible to avoid the rearrangement under non-acidic conditions; when therefore **36** was treated with *n*-PrSLi in HMPA, the non-rearranged product (**38**) was indeed obtained, but even at 38 °C where the reaction is quite slow, 5% of **37** was still formed.

The biological activity of the new huperzine A analogues described herein will be reported separately.

ACKNOWLEDGMENT

We are indebted to the National Institutes on Aging for support of this research.

EXPERIMENTAL SECTION

5-Ethylenedioxy-2-hydroxycyclohex-1-enecarboxylic Acid Methyl Ester (5). To 28.5 g (250 mmol) of a 35% suspension of potassium hydride in mineral oil which had previously been washed with THF was added 500 ml of dry dimethyl carbonate. The suspension was heated to reflux, and with continued gentle heating a solution of 19.5 g (125 mmol) of **4** in 200 ml of dry dimethyl carbonate was added dropwise within 75 min. The reaction mixture was refluxed for 3 h, then allowed to return to 23 °C, and 50 ml of methanol was added cautiously with ice cooling, followed by 100 ml of 20% aqueous NH_4Cl. After evaporation to a small volume, enough water was added to dissolve the salts, and the mixture was extracted with two 100 ml portions of CH_2Cl_2. Drying over $MgSO_4$ and evaporation yielded 28.6 g of the crude product as a turbid yellow oil which was used in the subsequent step without further purification. The crude product could not be crystallized directly but the analyical sample was readily obtained by column chromatography on silica gel with ethyl acetate/hexane 1:5, followed by crystallization from a small volume of hexane (+23 to -15 °C): mp 61-63.5 °C after sintering. In $CDCl_3$ solution, the compound exists as a 5:1 mixture of enol and keto tautomers. ^{1}H Nmr ($CDCl_3$) both tautomers δ 4.07-3.98 (m, 4 H); enol tautomer δ 12.15 (s, 1 H), 3.74 (s, 3 H), 2.51 (t, 2 H, J = 7 Hz), 2.47 (s, 2 H), 1.84 (t, 2 H, J = 7 Hz); keto tautomer δ 3.68 (dd, 1 H, J = 6, 11 Hz), 2.73-2.56 (m, 2 H), 2.42 (m, 1 H), 2.15 (m, 1 H), 2.05 (m, 1 H); ^{13}C nmr ($CDCl_3$) δ 204.71, 172.52, 171.24, 169.82, 107.27, 106.65, 95.25, 64.87, 64.82, 64.62, 53.94, 52.30, 51.54, 38.19, 36.59, 34.43, 32.69, 30.38, 27.95; ir (film) 2955, 1747, 1719, 1661, 1618, 1292, 1233, 1196, 1061 cm^{-1}; ms (EI) *m/z* 214 (M^+, 20%), 182, 99, 86 (100%).

7-Ethylenedioxy-3-methylene-9-oxobicyclo[3.3.1]nonane-1-carboxylic Acid Methyl Ester (6). 23.5 mg (0.1 mmol) of $Pd(OAc)_2$ and 110 mg (0.42 mmol) of PPh_3 were stirred at 23 °C in 7 ml of degassed dry dioxane under argon for 30 min. A solution of 450 mg (2.1 mmol) of **5**, 0.31 ml (2.1 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 336 µl (2.1 mmol) of 2-methylene-1,3-propanediol diacetate in 3 ml of degassed dry dioxane was added dropwise to the complex thus obtained over a period of 10 min. After stirring for 20 min at 23 °C, a solution of 0.34 ml (2.3 mmol) of DBU in 2 ml of degassed dry dioxane was added dropwise. Stirring at 23 °C was continued for 20 min, then the mixture was refluxed for 5 h and finally stirred at 23 °C for 12 h. Concentration and chromatography on silica gel with ethyl acetate/hexane 1:4 gave 370 mg (66%) of **6** as a colorless oil: ^{1}H Nmr ($CDCl_3$) δ 5.10 (m, 2 H), 4.10-3.90 (m, 4 H), 3.78 (s, 3 H), 3.02 (d, 1 H J = 14 Hz), 2.77-2.70 (m, 2 H), 2.65-2.58 (m, 1 H), 2.50 (dd, 1 H, J = 3, 8.5 Hz), 2.42 (dt, 1 H, J = 3, 13.5 Hz), 2.24-2.08 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 210.60, 171.98, 139.00, 117.89, 104.74, 65.15, 64.28, 57.13, 52.70, 46.65, 44.15, 43.64, 39.88, 38.77; ir (film) 1739, 1730, 1435, 1116 cm^{-1}; ms *m/z* 266 (M^+, 100%), 235, 211, 207, 179, 151; hrms calcd for $C_{14}H_{18}O_5$ 266.1149, found 266.1155.

3-Ethylenedioxy-6-(methanesulfonyloxy)-7-methyl-9-oxobicyclo[3.3.1]nonane-1-carboxylic Acid Methyl Ester (8). The above crude product and 1.9 ml (15 mmol) of 1,1,3,3-tetramethylguanidine were dissolved in

200 ml of DMF. At 0 °C, a solution of 20.7 ml (250 mmol) of methacrolein in 50 ml of DMF was added in 10 min. The mixture was stirred at 23 °C for 25 h, then the volatiles were pumped off, and the residue was dissolved in a small volume of CH_2Cl_2 and filtered over 100 g of silica gel with ethyl acetate/hexane 1:1. After evaporation, the crude product together with 1.8 g (15 mmol) of 4-(dimethylamino)pyridine (DMAP) and 28 ml (0.2 mol) of triethylamine were dissolved in 300 ml of dry CH_2Cl_2. The solution was cooled in an ice bath, and 14 ml (0.18 mmol) of $MeSO_2Cl$ in 50 ml of CH_2Cl_2 was added dropwise within 100 min. The mixture was stirred at 23 °C for 2.5 h, then recooled to 0 °C, and 10 ml of water was added. After stirring overnight at 23 °C, the phases were separated, and the organic phase was successively washed with 200 ml of 10% aqueous $KHSO_4$, 20 ml of water, and 20 ml of saturated aqueous $NaHCO_3$. After drying over $MgSO_4$, 100 g of silica gel was added, and the solvent was evaporated. The residue was chromatographed on 150 g of silica gel with ethyl acetate/hexane 1:2 (to remove a forerun), then 7:3 to obtain 35.2 g (nominally 78% from **4**) of crude mesylate which was used in the subsequent reaction without further purification. Analytical samples of the two major isomers were obtained by chromatography on silica gel with ethyl acetate/hexane 2:3, then 1:1, finally 3:2 as eluent, followed by crystallization from CH_2Cl_2/hexane. Less polar isomer: mp 128 °C; ^{1}H nmr ($CDCl_3$) δ 5.20 (dd, 1 H, J = 1.5, 11.5 Hz), 4.19-4.04 (m, 2 H), 3.95-3.83 (m, 2 H), 3.78 (s, 3 H), 3.04 (s, 3 H), 2.82 (narrow m, 1 H), 2.62, 2.12 (ABq, 2 H, J = 14.5 Hz, B part split into d with J = 4 Hz), 2.58-2.48 (m, 2 H), 2.37 (t, 1 H, J = 13.5 Hz), 2.17 (dd, 1 H, J = 5, 15 Hz), 1.69 (m, 1 H), 1.14 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 208.50, 171.91, 106.59, 84.62, 64 96, 63.59, 55.79, 52.79, 44.38, 39.97, 38.44, 33.95, 32.76, 17.75; ir (KBr) 1744, 1723, 1358, 1175, 1042, 932, 841, 529 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_8S$: C, 49.72; H, 6.12. Found: C, 49.46; H, 5.91. More polar isomer: mp 177-179 °C; ^{1}H nmr ($CDCl_3$) δ 4.41 (dd, 1 H, J = 5, 10.5 Hz), 4.09-3.94 (m, 4 H), 3.79 (s, 3 H), 3.27 (ddd, 1 H, J = 3.5, 5, 10.5 Hz), 3.04 (s, 3 H), 2.89, 2.17 (ABq, 2 H, J = 14.5 Hz, A part split into d with J = 3.5 Hz), 2.55, 2.17 (ABq, 2 H, J = 14.5 Hz, A and B parts split into d and dd with J = 3.5 and 3.5, 10.5 Hz, resp.), 2.50 (m, 1 H), 2.00, 1.90 (ABq, 2 H, J = 14 Hz, A and B parts split into d with J = 5.5 and 12.5 Hz, resp.), 1.18 (d, 3 H, J = 6.5 Hz); ^{13}C nmr ($CDCl_3$) δ 205.02, 171.52, 104.67, 85.32, 65.45, 64.46, 56 51, 52.91, 49.31, 41.08, 39.24, 38.74, 34.57, 28.76, 17.13; ir (KBr) 1726, 1364, 1344, 1177, 943, 529 cm^{-1}; ms (EI) *m/z* 362 (M^+, 14%), 330, 303, 267, 207, 99 (99%), 86 (100%).

7-Ethylenedioxy-3-methyl-9-oxobicyclo[3.3.1]non-3-ene-1-carboxylic Acid Methyl Ester (9) A solution of 9.22 g (25.4 mmol) of **8** in 100 ml of 2,4,6-collidine was refluxed under argon for 24 h. After cooling, the solution was decanted from a tarry precipitate, and the solvent was pumped off. Both the precipitate and the distillation residue were taken up in a total of 10 ml of methanol, and 50 ml of CH_2Cl_2 was added. This solution was washed with two 50 ml portions of 5% H_3PO_4 (addition of a small volume of brine accelerates phase separation), then with 30 ml of brine, and finally with 15 ml of saturated $NaHCO_3$ solution. After evaporation together with 30 g of silica gel, the residue was chromatographed on silica gel with ethyl acetate/hexane 2:3 to obtain 2.19 g (32%) of **9** as an amber syrup. The analytical sample was obtained by bulb-to-bulb distillation (oven temperature 150 °C/ 0.05 torr) as a yellowish syrup: ^{1}H Nmr ($CDCl_3$) δ 5.37 (br d, 1 H, J = 6 Hz), 4.06-3.80 (m, 4 H), 3.79 (s, 3 H), 3.29, 2.61 (ABq, 2 H, J = 18 Hz, A part br), 2.83 (narrow m, 1 H), 2.75, 2.18 (ABq, 2 H, J = 14 Hz, B part split into d with J = 3 Hz), 2.25, 2.10 (ABq, 2 H, J = 14 Hz, A and B parts split into d and dd with J = 5.5 and 2.5, 3.5 Hz, resp.), 1.73 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 209.71, 171.85, 135.68, 121.58, 106.65, 65.21, 63.40, 56.29, 52.72, 44.80, 44.40, 43.70, 41.21, 22.33; ir (film) 1742, 1726, 1435, 1250, 1053,

822 cm^{-1}; ms (EI) *m/z* 266 (M^+, 74%), 234, 207, 91, 87, 86 (100%). Anal. Calcd for $C_{16}H_{22}O_4$: C, 63.15; H, 6.81. Found: C, 63.20; H, 7.02.

(1*RS*,3*RS*,5*SR*,7*SR*,8*RS*)-8-Bromo-3-(2-bromoethyl)-1-methyl-6-oxo-2-oxaadamantane-5-carboxylic Acid Methyl Ester (11). To a solution of 122 mg (458 mmol) of **9** in 5 ml of CH_2Cl_2 was added dropwise at -78 °C a dilute solution of bromine in CH_2Cl_2 until the orange color persisted. After evaporation and drying in vacuo, the resulting yellowish solid was recrystallized from a small volume of hot $CHCl_3$ to which hexane was added, to obtain 135 mg (69%) of colorless crystals: mp 134-135.5 °C; ^1H nmr ($CDCl_3$) δ 4.30 (t, 1 H, *J* = 3 Hz), 4.04-3.87 (m, 2 H), 3.80 (s, 3 H), 3.46 (t, 2 H, *J* = 6.5 Hz), 3.14-3.05 (m, 2 H), 2 50 (dd, 1 H, *J* = 2, 13 Hz), 2 37 (ddd, 1 H, *J* = 3, 4.5, 13 Hz), 2.19 (dd, 1 H, *J* = 3.5, 13 Hz), 2.15 (dd, 1 H, *J* = 4.5, 13 Hz), 1.86 (dd, 1 H, *J* = 3, 14 Hz), 1.46 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 204.82, 169.73, 96.28, 76.42, 62.59, 58.04, 56.79, 53.23, 52.66, 42.40, 40.87, 38.91, 30.32, 26.00; ir (KBr) 1748, 1724, 1279, 1121, 1051, 1005 cm^{-1}; ms (EI) *m/z* 428/426/424 (M^+, 2/5/3%), 369/367/365, 347/345, 319/317, 287/285, 221, 193, 189, 161 (100%), 133, 109/107; hrms (M + H^+, $C_{14}H_{19}O_5{}^{79}Br{}^{81}Br$) calcd 426.9579, found 426.9640.

(1*RS*,3*RS*,5*SR*,7*SR*,8*RS*)-8-Bromo-3-(2-iodoethyl)-1-methyl-6-oxo-2-oxaadamantane-5-carboxylic Acid Methyl Ester (12). A solution of 21.9 mg (51.4 μmol) of **11** and 38 mg (0.25 mmol) of NaI in 0.5 ml of butanone was heated to 65 °C for 130 min. The reaction mixture was directly applied on a silica gel column, and the product was eluted with ethyl acetate/hexane 1:3 to obtain 22.8 mg (94%) of a colorless solid. The analytical sample was recrystallized from $CHCl_3$/hexane: mp 155-157 °C; ^1H nmr ($CDCl_3$) δ 4.29 (t, 1 H, *J* = 3 Hz), 3.97-3.85 (m, 2 H), 3.80 (s, 3 H), 3.24 (t, 2 H, *J* = 7 Hz), 3.14-3.05 (m, 2 H), 2.49 (dd, 1 H, *J* = 2, 13 Hz), 2.36 (ddd, 1 H, *J* = 3, 4.5, 13 Hz), 2.18 (dd, 1 H, *J* = 4, 13 Hz), 2.15 (dd, 1 H, *J* = 4.5, 13 Hz), 1.86 (dd, 1 H, *J* = 3, 14 Hz), 1.46 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 204.87, 169.79, 96 28, 76.45, 63.54, 58.10, 56.85, 53.29, 52.72, 42.51, 41 00, 38.96, 26.06, 2.89; ir (KBr) 1746, 1723, 1277, 1119, 1051, 1005 cm^{-1}; ms (EI) *m/z* 474/472 (M^+, 5/5%), 446/444, 393, 365, 161, 155 (100%); hrms (M + H^+, $C_{14}H_{19}O_5{}^{79}BrI$) calcd 472.9461, found 472.9461.

(1*RS*,3*RS*,5*SR*,7*SR*,8*RS*)-8-Chloro-3-(2-chloroethyl)-1-methyl-6-oxo-2-oxaadamantane-5-carboxylic Acid Methyl Ester (13). To a solution of 66 mg (248 μmol) of **9** in 1 ml of CH_2Cl_2 was added dropwise at -78 °C a solution of 40 μl (0.5 mmol) of SO_2Cl_2 in 1 ml of CH_2Cl_2. The reaction mixture was allowed to reach 0 °C within 35 min. After evaporation, the residue was chromatographed on silica gel with ethyl acetate/hexane 1:4. The product was twice recrystallized from a small volume of hot $CHCl_3$ to which hexane was added, to obtain 42 mg (50%) of colorless crystals: mp 124-125 °C; ^1H nmr ($CDCl_3$) δ 4.18 (t, 1 H, *J* = 3 Hz), 3.93-3.85 (m, 2 H), 3.80 (s, 3 H), 3.63 (t, 2 H, *J* = 6 Hz), 3.02-2.96 (m, 2 H), 2.50 (dd, 1 H, *J* = 2, 13 Hz), 2.35 (ddd, 1 H, *J* = 3, 4.5, 13 Hz), 2.22 (dd, 1 H, *J* = 4, 13 Hz), 2.16 (dd, 1 H, *J* = 4.5, 13 Hz), 1.82 (dd, 1 H, *J* = 3, 14 Hz), 1.43 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 205.01, 169.79, 96.16, 76.56, 66.33, 62.72, 56.73, 52.63, 52.55, 42.82, 41.50, 40.65, 38.41, 24.94; ir (KBr) 1740, 1724, 1279, 1127, 976 cm^{-1}; ms (EI) *m/z* 340/338/336 (M^+, 1/7/12%), 312/310/308, 303/301, 275/273, 243/241, 215/213, 161 (100%), 133; hrms (M + H^+, $C_{14}H_{19}O_5{}^{35}Cl_2$) calcd 337.0610, found 337.0599.

(*Z*)-7-Ethylenedioxy-9-ethylidene-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylic Acid Methyl Ester (14). Under argon and with ice cooling, 24 ml (60 mmol) of *n*-BuLi (2.5 M in hexane) was added dropwise within 30 min to 24.5 g (66 mmol) of $EtPPh_3Br$ in 200 ml of THF. The intensely orange-colored mixture was stirred at 0 °C for 35 min, then a solution of 5.35 g (20.1 mmol) of **9** in 50 ml of THF was added dropwise in 35 min. Stirring was continued for 45 min at 0 °C, then for 2.5 h at 23 °C whereon the excess of the ylide was quenched by addition of 2 ml of water. The mixture was evaporated after addition of 100 g of silica gel, and the residue was filtered over a short silica gel column using ethyl acetate/hexane 1:8, later 1:5 as the eluent. Evaporation and drying in vacuo yielded 3.65 g (65%) of the product as a yellowish waxy solid consisting (^{1}H nmr) of a 82:18 mixture of *Z* and *E* isomers. The analytical sample was obtained by bulb-to-bulb distillation (oven 150 °C/0.05 torr) as a colorless wax: mp 63-71 °C; ^{1}H nmr ($CDCl_3$) (*Z* isomer only) δ 5.44 (q, 1 H, *J* = 7 Hz), 5.43 (br, 1 H), 4.02-3.75 (m, 4 H), 3.74 (s, 3 H), 2.99 (d, 1 H, *J* = 17.5 Hz), 2.80 (br, 1 H), 2.40 (dd, 1 H, *J* = 1, 14 Hz), 2.12 (d, 1 H, *J* = 17.5 Hz), 1.98-1.78 (m, 3 H), 1.67 (s, 3 H), 1.44 (d, 3 H, *J* = 7 Hz); ^{13}C nmr ($CDCl_3$) (*Z* isomer only) δ 176.74, 137.80, 133.60, 123.86, 115.41, 108.52, 64.85, 62.92, 52.08, 47.08, 45.32, 43.57, 41.84, 41.01, 22.52, 12.39; ir (film) 2920, 1730, 1433, 1238, 1055 cm^{-1}, ms (EI) *m/z* 278 (M^+, 16%), 219, 177, 145, 133. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.91; H, 7.91.

(*E*)-7-Ethylenedioxy-9-ethylidene-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylic Acid Methyl Ester (15). A solution of 3.65 g (13.1 mmol) of **14**, 2.7 ml (26.2 mmol) of thiophenol, and 2.15 g (13.1 mmol) of azobis(isobutyronitrile) (AIBN) in 26 ml of toluene was stirred under argon at 90-95 °C for 17 h. After cooling, the same amounts as above of thiophenol and AIBN were added, and the reaction was continued under the same conditions for 18.5 h. The solvent was pumped off, and the residue was chromatographed on silica gel with ethyl acetate/hexane 1:10 to obtain, after evaporation and drying in vacuo, 3.44 g (94%) of **15** as a light-yellow syrup. The *E*/*Z* ratio (by gc-ms) is 97:3. The analytical sample was obtained by bulb-to-bulb distillation (oven 150 °C/0.07 torr) as a colorless syrup: ^{1}H Nmr ($CDCl_3$) (*E* isomer only) δ 5.42 (dd, 1 H, *J* = 1.5, 6 Hz), 4.95 (q, 1 H, *J* = 7 Hz), 4.04-3.73 (m, 4 H), 3.75 (s, 3 H), 3.34 (br, 1 H), 2.96 (d, 1 H, *J* = 17.5 Hz), 2.37 (dd, 1 H, *J* = 1.5, 14 Hz), 2.12 (d, 1 H, *J* = 17.5 Hz), 1.95 (dd, 1 H, *J* = 2, 14 Hz), 1.92-1.80 (m, 2 H), 1.63 (d, 3 H, *J* = 6.5 Hz), 1.55 (s, 3 H); ^{13}C nmr ($CDCl_3$) (*E* isomer only) δ 175.65, 139.22, 134.52, 122.60, 113.54, 108.72, 64.96, 62.94, 52.05, 50.76, 45.44, 41.53, 40.25, 32.17, 22.68, 13.09; ir (film) 2922, 1730, 1433, 1238, 1053 cm^{-1}; ms (EI) *m/z* 278 (M^+, 22%), 219, 177, 145, 133. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found. C, 68.94; H, 7.90.

(*E*)-9-Ethylidene-3-methyl-7-oxobicyclo[3.3.1]non-3-ene-1-carboxylic Acid Methyl Ester (16). A solution of 3.36 g (12.1 mmol) of **15** in 84 ml of methanol and 28 ml of 5% HCl was refluxed for 4 h. The mixture was partially evaporated to remove methanol and extracted with one 50 ml portion and two 20 ml portions of ethyl acetate. After drying over $MgSO_4$ and evaporation, the residue was chromatographed on silica gel with ethyl acetate/hexane 1:9 to obtain 2.22 g (78%) of **16** as a yellowish, somewhat waxy solid (*E*/*Z* ratio 96:4 by gc-ms). The analytical sample was purified by bulb-to-bulb distillation (oven 130 °C/0.05 torr): mp 76-79 °C; ^{1}H nmr ($CDCl_3$) (*E* isomer only) δ 5.40 (br d, 1 H, *J* = 5.5 Hz), 5.17 (q, 1 H, *J* = 6.5 Hz), 3.80 (s, 3 H), 3.57 (br, 1 H), 3.15 (dd, 1 H, *J* = 2, 16 Hz), 3.04 (d, 1 H, *J* = 17.5 Hz), 2.54-2.40 (m, 2 H), 2.39 (dd, 1 H, *J* = 2, 16 Hz), 2.06 (d, 1 H, *J* = 17 5 Hz), 1.73 (d, 3 H, *J* = 6.5 Hz), 1.64 (s, 3 H); ^{13}C nmr ($CDCl_3$) (*E* isomer only) δ 209.25, 174.23,

137.02, 132.93, 123.63, 116.47, 52.54, 52.38, 52.01, 46.86, 42.48, 33.47, 22.58, 13.17; ir (film) 1726, 1715, 1439, 1231 cm^{-1}; ms (EI) *m/z* 234 (M^+, 2%), 202, 177, 175, 145 (100%), 105, 91. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71 77; H, 7.74. Found: C, 71.65; H, 7.78.

(*E*)-9-Ethylidene-3-methyl-7-oxobicyclo[3.3.1]non-3-ene-1-carboxylic Acid (17). A solution of 418 mg (1.78 mmol) of **16** in 3 6 ml each of THF and methanol was stirred at 23 °C with 3.6 ml of 1.0 M NaOH for 14 h. The mixture was evaporated to a small volume, diluted with 10 ml of water, and washed with 20 ml of ethyl acetate. After acidification with 1 ml of 5 M HCl, the aqueous phase was extracted with 3 x 10 ml of CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated, and the residue was dissolved in 1 ml of CH_2Cl_2 Addition of 5 ml of hexane induced crystallization which was allowed to proceed first at 23 °C, then at -15 °C to obtain 349 mg (89%) of the acid as colorless crystals: mp 157-158.5 °C; ^1H nmr ($CDCl_3$) δ 5.47-5.40 (m, 2 H), 3.60 (br, 1 H), 3.14 (dd, 1 H, *J* = 1.5, 15.5 Hz), 3.03 (d, *J* = 18 Hz), 2.52-2.43 (m, 3 H), 2.12 (d, 1 H, *J* = 17 5 Hz), 1.77 (d, 3 H, *J* = 6.5 Hz), 1.65 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 209.45, 179.67, 136.16, 132.78, 123.72, 116.91, 52.38, 51.75, 46.89, 42.36, 33.46, 22.63, 13.26; ir (KBr) 1711, 1694, 1437, 1412, 1283, 1260, 949, 818, 725 cm^{-1}; ms (EI) *m/z* 220 (M^+, 10%), 202, 175, 163, 145 (100%), 105. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.77; H, 7.35.

(*E*)-(9-Ethylidene-3-methyl-7-oxobicyclo[3.3.1]non-3-en-1-yl)carbamic Acid Methyl Ester (3). To 307 mg (1.39 mmol) of **17** in 4 ml of chlorobenzene was added 198 ml (1.42 mmol) of triethylamine, followed by 302 ml (1.40 mmol) of diphenylphosphoryl azide. The mixture was heated to 90 °C for 3.5 h. After cooling, 8 mL of dry methanol was added, and the mixture was refluxed for 8.5 h. Evaporation was followed by column chromatography (silica gel, ethyl acetate/CH_2Cl_2 10:1, then 5:1) to obtain 314 mg (90%) of the product as a yellowish glass which slowly solidified. The analytical sample was obtained by bulb-to-bulb distillation (oven 170 °C/0.05 torr): mp 122.5-123.5 °C; ^1H nmr ($CDCl_3$) δ 5.46 (q, 1 H, *J* = 7 Hz), 5.39 (br d, 1 H, *J* = 5.5 Hz), 4.75 (br s, 1 H), 3.67 (s, 3 H), 3.59 (narrow m, 1 H), 3.44 (br d, 1 H, *J* = 12.5 Hz), 2.56-2.37 (m, 3 H), 2.33 (s, 2 H), 1.75 (d, 3 H, *J* = 7 Hz), 1.61 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 208.83, 155.20, 136.30, 132.31, 124.75, 114.10, 58.04, 53.23, 51.98, 47.75, 46.26, 33.22, 22.37, 12.95; ir (film) 3339, 1713, 1537, 1262, 665 cm^{-1}; ms (EI) *m/z* 249 (M^+, 5%), 234, 217, 206, 192 (100%), 174, 160; HRMS (M + H^+, $C_{14}H_{20}NO_3$) calcd 250.1443, found 250.1435.

(1*RS*,5*SR*,7*SR*,9*E*)-9-Ethylidene-7-hydroxy-3-methylbicyclo[3.3.1]non-3-ene-1-carboxylic Acid Methyl Ester (18). To a solution of 36.6 mg (156 μmol) of **16** in 0.83 ml of methanol was added with ice cooling $NaBH_4$ in small portions until tlc (silica gel, ethyl acetate/hexane 1:6) showed complete conversion to the more polar product. The reaction mixture was evaporated and the residue chromatographed on silica gel with ethyl acetate/hexane 1:4 to obtain 29.3 mg (79%) of the title compound as a colorless syrup: ^1H Nmr ($CDCl_3$) δ 5.76 (br d, 1 H, *J* = 5 Hz), 4.93 (q, 1 H, *J* = 6.5 Hz), 4.06 (br, 1 H), 3.77 (s, 3 H), 3.32 (br, 1 H), 3.07 (d, 1 H, *J* = 18 Hz), 2.88 (br d, 1 H, *J* = 9.5 Hz), 2.55 and 2.06 (ABq, 2 H, *J* = 14.5 Hz, A ans B parts split into dd and t with *J* = 1.5, 5 and *J* = 2.5 Hz, resp.), 2.26 (d, 1 H, *J* = 18 Hz), 1.99 and 1.83 (ABq, 2 H, *J* = 14 Hz, A and B parts split into q and t with *J* = 2.5 and 5 Hz, resp.), 1.71 (s, 3 H), 1.60 (d, 3 H, *J* = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 175.84, 139.25, 135.15, 127.33, 113.45, 66.88, 52.08, 49.98, 44.32, 42.17, 37.88, 31.70, 22.79, 12.89; ir (film) 3432,

2928, 1730, 1435, 1238, 1217 cm^{-1}; ms (EI) *m/z* 236 (M^+, 15%), 218, 177, 159 (100%); hrms (M + H^+, $C_{14}H_{21}O_3$) calcd 237.1491, found 237.1502.

(1*RS*,3*RS*,5*SR*,6*E*,7*SR*,8*RS*)-6-Ethylidene-8-iodo-1-methyl-2-oxaadamantane-5-carboxylic Acid Methyl Ester (19). To a mixture of 39.4 mg (167 μmol) of **18** in 1 ml of ether and 0.3 ml of saturated $NaHCO_3$ solution was added at 23 °C 84 mg (0.33 μmol) of iodine. The reaction was allowed to proceed at 23 °C for 30 min, then sufficient saturated $Na_2S_2O_3$ solution was added to discharge the iodine color, and the entire mixture was applied on a short silica gel column. Elution with ethyl acetate/hexane 1:5 furnished 49.5 mg (82%) of the title compound as a colorless solid: mp 96-101 °C (from hexane); ^1H nmr ($CDCl_3$) δ 5.24 (q, 1 H, *J* = 6.5 Hz), 4.58 (t, 1 H, *J* = 2.5 Hz), 4.28 (br, 1 H), 3.78 (s, 3 H), 3.43 (q, 1 H, *J* = 3 Hz), 2.85 (dd, 1 H, *J* = 2, 13 Hz), 2.35 and 1.74 (ABq, 2 H, *J* = 13 Hz, A and B parts split into q and dd with *J* = 4 and 1.5, 4 Hz, resp.), 2.12 and 2.00 (ABq, 2 H, *J* = 13 Hz, A and B parts split into t and dd with *J* = 2 and 2.5, 4 Hz, resp.), approx. 1.67 (dd, 1 H, partially overlapping, *J* = 2 Hz, second coupling not readable), 1.64 (d, 3 H, *J* = 6.5 Hz), 1.33 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 175.36, 136.72, 118.62, 73.21, 68.97, 51.94, 48.64, 43.34, 40.80, 39.49, 39.22, 38.86, 29.15, 12 61; ir (film) 2930, 1732, 1443, 1254, 1134, 1009, 665 cm^{-1}; ms (EI) *m/z* 362 (M^+, 1%), 331, 303, 259, 235 (100%), 203, 175; hrms (M + H^+, $C_{14}H_{20}O_3I$) calcd 363.0457, found 363.0476.

(1*RS*,5*SR*,7*RS*,9*E*)-(7-Amino-9-ethylidene-3-methylbicyclo[3.3.1]non-3-en-1-yl)carbamic Acid Methyl Ester (22). A solution of 35.6 mg (143 μmol) of **3**, 29 μl (0.57 mmol) of $MeONH_2$, and 2.5 μl (44 μmol) of acetic acid in 200 μl of methanol was kept at 23 °C for 2 h. After evaporation, the residue was taken up in 1.5 ml of THF, added to a mixture of 15 ml of liquid ammonia and 1 ml of methanol, and reduced with 0.28 g (12.2 mmol) of sodium metal as described below for the preparation of **25**. After evaporation of the ammonia, 5 ml of water was added, and the product was extracted into 4 x 8 ml of ethyl acetate. Drying over Na_2SO_4, evaporation, and filtration over silica gel half-saturated with ammonia using CH_2Cl_2/methanol 9:1 as the eluent yielded 32.7 mg (91% over both steps) of **22** as a colorless glass: ^1H Nmr ($CDCl_3$) δ 5.36 (br d, 1 H, *J* = 5.5 Hz), 5.16 (q, 1 H, *J* = 6.5 Hz), 3.65 (s, 3 H), 3.38 (narrow m, 1 H), 3.25 (br, 1 H, C*H*NH_2, $W_{1/2}$ = 35 Hz, unchanged after addition of D_2O), 2.69, 2.45 (ABq, 2 H, *J* = 18 Hz, A part br), 2.27 (br dd, 1 H, *J* = 3.5, 11.5 Hz), 1.88 (br d, 1 H, *J* = 12 Hz), 1.7 (br, 2 H), 1.66 (d, 3 H, *J* = 7 Hz), 1.64 (s, 3 H), 1.46 (br t, 1 H, *J* = 11.5 Hz), 1.15 (dt, 1 H, *J* = 3.5, 11.5 Hz); ^{13}C nmr ($CDCl_3$) δ 155.4 (br), 139.59, 134.90, 123.55, 110.22, 56.90, 51.71, 45.24, 44.41, 40.8 (br), 33.84, 29.73, 22.18, 12.78; ir (film) 3343, 2926, 1724, 1537, 1250 cm^{-1}; ms (EI) *m/z* 250 (M^+, 31%), 235, 193, 175, 160 (100%); hrms (M + H^+, $C_{14}H_{23}N_2O_2$) calcd 251.1760, found 251.1744.

(1*RS*,5*SR*,7*RS*,9*E*)-[7-(*N*-Acetylamino)-9-ethylidene-3-methylbicyclo[3.3.1]non-3-en-1-yl]carbamic Acid Methyl Ester (23). To a solution of 120 mg (479 μmol) of **22** in 1.45 ml of pyridine was added 135 μl (1.43 mmol) of acetic anhydride, and the mixture was stirred at 23 °C for 2.5 h. Evaporation was followed by filtration over silica gel with acetone/hexane 1:1. The eluate was evaporated, and the residue was crystallized from CH_2Cl_2/hexane to obtain 116 mg (83%) of the amide. The analytical sample was obtained by several recrystallizations from the same solvent mixture: mp 196-198 °C; ^1H nmr ($CDCl_3$) δ 5.36 (br dd, 1 H, *J* = 1, 6 Hz), 5.21 (overlapping, 1 H), 5.19 (q, 1 H, *J* = 6.5 Hz), 4.70 (br s, 1 H), 4.39 (m, 1 H), 3.64 (s, 3 H), 3.40 (narrow m, 1 H), 2.51, 2.43 (ABq, 2 H, *J* = 17.5 Hz), 2.26 (ddd, 1 H, *J* = 1.5, 5, 12 Hz), 1.97 (m, 1 H), 1.91 (s, 3

H), 1.82 (m, 1 H), 1.67 (s, 3 H), 1.66 (d, 3 H, J = 6.5 Hz), 1.21 (dt, 1 H, J = 3.5 Hz (d), 12 Hz (t)); ^{13}C nmr ($CDCl_3$) δ 169.15, 155.3 (br), 138.83, 135.04, 123.33, 110.95, 56.96, 51.79, 46.4 (br), 46.17, 43.09, 36.95, 33.64, 23.59, 22.26, 12.78; ir (film) 3306, 2930, 1715, 1651, 1539, 731 cm^{-1}; ms (EI) *m/z* 292 (M^+, 20%), 233, 158, 143, 132 (100%). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.27; H, 8.27, N, 9.45.

(1*RS*,5*SR*,7*RS*,9*E*)-(9-Ethylidene-7-hydroxy-3-methylbicyclo[3.3.1]non-3-en-1-yl)carbamic Acid Methyl Ester (25). To a solution of 63.4 mg (254 μmol) of **3** in 10 ml of liquid ammonia, 1.5 ml of THF, and 1 ml of methanol was added at -78 °C in several portions within 20 min 312 mg (13.5 mmol) of sodium metal. The mixture was stirred in the cold bath until its blue color had faded, then the ammonia was allowed to evaporate. The residue was partitioned between 10 ml of water and 20 ml of ether, and the aqueous phase was extracted with 2 x 10 ml of ether. After drying over $MgSO_4$ and evaporation, the residue was filtered over silica gel with ethyl acetate/hexane 1:1 to obtain 65.2 mg (102%) of **25** as a colorless glass: ^{1}H Nmr($CDCl_3$) δ 5.38 (br d, 1 H, J = 5.5 Hz), 5.19 (q, 1 H, J = 7 Hz), 4.82 (br s, 1 H), 4.15 (tt, 1 H, J = 5.5, 11 Hz), 3.65 (s, 3 H), 3.38 (narrow m, 1 H), 2.65, 2.46 (br ABq, J = 17.5 Hz), 2.44 (ddd, 1 H, J = 1.5, 5, 11.5 Hz), 2.03 (m, 1 H), 1.67 (d, 3 H, J = 7 Hz), approx. 1.65 (2 H, concealed), 1.63 (s, 3 H), 1.30 (dt, 1 H, J = 4 Hz (d), 9 Hz (t)); ^{13}C nmr ($CDCl_3$) δ 155.5 (br), 139.14, 134.62, 123.58, 110.75, 65.57, 56.84, 51.80, 50.12, 45.45, 39.46, 33.28, 22.18, 12.84; ir (film) 3341, 2930, 1713, 1516, 1262, 1028, 733 cm^{-1}; ms (EI) *m/z* 251 (M^+, 10%), 236, 233, 222, 176, 158, 143, 117, 91, 59 (100%); hrms (M + H^+, $C_{14}H_{22}NO_3$) calcd 252.1600, found 252.1585.

(1*RS*,5*SR*,7*RS*,9*E*)-[7-((*N*,*N*-Dimethylcarbamoyl)oxy)-9-ethylidene-3-methylbicyclo[3.3.1]non-3-en-1-yl]carbamic Acid Methyl Ester (26). A solution of 46.2 mg (184 μmol) of **25** in 1 ml of THF was added dropwise at 0 °C under argon to 74 mg (1.85 mmol) of NaH (60% dispersion in oil, which was removed by washing with THF). After 10 min at 23 °C, 85 μl (0.92 mmol) of neat *N*,*N*-dimethylcarbamoyl chloride was added dropwise The mixture was stirred at 23 °C for 9 h, after which period 0.3 ml of water was added cautiously, and evaporated. The residue was filtered over silica gel with ethyl acetate/hexane (1:2, then 1:1, finally 2:1) to obtain 12.5 mg (27%) of starting material, followed by 43.2 mg (73%) of **26** which forms a colorless glass: ^{1}H Nmr ($CDCl_3$) δ 5.40 (br d, 1 H, J = 6 Hz), 5.21 (q, 1 H, J = 6.5 Hz), 5.13 (tt, 1 H, J = 5.5, 11 Hz), 4.78 (br s, 1 H), 3.65 (s, 3 H), 3.40 (narrow m, 1 H), 2 87 (br s, 3 H), 2.83 (br s, 3 H), 2.57, 2.49 (ABq, 2 H, J = 17.5 Hz, A part br), 2.38 (ddd, 1 H, J = 2, 5.5, 11.5 Hz), 2.07 (m, 1H), 1.91 (br t, 1 H, J = 11.5 Hz), 1.67 (d, 3 H, J = 6 Hz), 1.65 (s, 3 H), 1.40 (dt, 1 H, J = 4 Hz (d), 11.5 Hz (t)); ^{13}C nmr ($CDCl_3$) δ 156.13, 155.3 (br), 138.89, 134.73, 123.23, 110.86, 69.45, 56.99, 51.71, 46.01, 45.72, 36.3 (br), 35.93, 35.8 (br), 33.11, 22.15, 12.75; ir (film) 3327, 2932, 1694, 1192, 731 cm^{-1}; ms (EI) *m/z* 322 (M^+, 5%), 233, 193 (100%), 160, 158, 143, 72; hrms (M + H^+, $C_{17}H_{27}N_2O_4$) calcd 323.1917, found 323.1977.

1*RS*,5*SR*,7*RS*,9*E*)-1-Amino-7-[(*N*,*N*-dimethylcarbamoyl)oxy]-9-ethylidene-3-methylbicyclo[3.3.1]non-3-ene (27). A solution of 13.4 mg (41.6 μmol) of **26** in 0.6 ml of dry HMPA was carefully degassed and placed under an argon atmosphere. After addition of 0.4 ml (1.24 mmol) of a 3.1 M solution of *n*-PrSLi in HMPA, the mixture was stirred at 90 °C for 3 h. The cooled solution was poured into 30 ml of water and extracted with 3 x 10 ml of ethyl acetate/methanol 19:1. The combined organic layers were washed with 15 ml of brine, dried over

$MgSO_4$, and evaporated. Twofold chromatography on silica gel with CH_2Cl_2/methanol (14:1, then 7:1) afforded 8.1 mg (74%) of the title compound as a glass: ^1H Nmr ($CDCl_3$) δ 5.41 (q, 1 H, J = 6.5 Hz), 5.38 (narrow, overlapping, 1 H), 5.13 (tt, 1 H, J = 5.5, 11 Hz), 3.40 (narrow m, 1 H), 2.88 (br s, 3 H), 2.84 (br s, 3 H), 2.31, 2.05 (ABq, 2 H, J = 17.5 Hz), 2.20 (ddd, 1 H, J = 2, 5.5, 11.5 Hz), 2.08 (m, overlapping, 1 H), 1.88 (br, 2 H), 1.67 (d, 3 H, J = 6.5 Hz), 1.63 (s, 3 H), 1.37 (dt, 1 H, J = 2 Hz (d), 11.5 Hz (t)), 1.33 (dt, 1 H, J = 4 Hz (d), 11.5 Hz (t)); ^{13}C nmr ($CDCl_3$) δ 156.29, 144.66, 135.15, 123.50, 110.00, 69.92, 54.03, 49.62, 48.64, 36.3 (br), 36.13, 35.8 (br), 33.56, 29.76, 22.26, 12.67; ir (film) 2928, 1699, 1397, 1192 cm^{-1}; ms (EI) *m/z* 264 (M^+, <1%), 175 (100%), 160 (98%), 146, 134, 120, 72; hrms (M + H^+, $C_{15}H_{25}N_2O_2$) calcd 265.1916, found 265.1893.

(1*RS*,4*RS*,5*SR*,9*E*)-9-Ethylidene-4-(methoxycarbonylthio)-3-methyl-7-oxobicyclo[3.3.1]non-2-ene-1-carboxylic Acid Methyl Ester (33). To 56.1 mg (239 μmol) of **16** in 0.24 ml of CH_2Cl_2 was added 24 μl (265 μmol) of neat ClSCOOMe. After standing at 23 °C for 22 h, the mixture was concentrated, and the residue was chromatographed on silica gel with ethyl acetate/hexane 1:8, then 1:6 to obtain, after a forerun, 35.6 mg (46%) of **33** as a colorless glass. It consists of two components in the ratio 92:8, presumably stereo- or regioisomers, barely separated on tlc. ^1H Nmr ($CDCl_3$) (major component) δ 5.55 (d, 1 H, J = 1 5 Hz), 5.44 (q, 1 H, J = 7 Hz), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.63 (dm, 1 H, J = 6 Hz (d)), 2.95, 2.51 (ABq, 2 H, J = 15 Hz, B part split into d with J = 1.5 Hz), 2.61-2.57 (m, 2 H), 1.79 (s, 3 H), 1.76 (d, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) (major component) δ 207.32, 173.02, 171.52, 132.87, 130.91, 129.10, 120.44, 54.39, 54.25, 52.66, 52.55, 50.20, 47.41, 39.36, 21.26, 13.37; ir (film) 2953, 1713, 1433, 1254, 1150, 675 cm^{-1}; ms (EI) *m/z* 324 (M^+, 6%), 292 (100%), 267, 235, 173 (88%), 163, 145 (92%), 131, 91, 59; hrms (M^+, $C_{16}H_{20}O_5S$) calcd 324.1032, found 324.1037.

(1*RS*,4*RS*,5*SR*,7*RS*,9*E*)-9-Ethylidene-7-(*N*-hydroxyamino)-4-(methoxycarbonylthio)-3-methylbicyclo-[3.3.1]non-2-ene-1-carboxylic Acid Methyl Ester (34). A solution of 24.2 mg (74.6 μmol) of **33**, 15 μl (0.3 mmol) of $MeONH_2$, and 2 μl (35 μmol) of acetic acid in 100 μl of methanol and 50 μl of CH_2Cl_2 was kept at 23 °C for 20.5 h. After evaporation, the residue was filtered over silica gel with ethyl acetate/hexane 1:9 to obtain 23.6 mg (89%) of the *O*-methyloxime which was immediately carried further on. Thus, to 12.2 mg (34.5 μmol) of the *O*-methyloxime in 100 μl of acetic acid was added 7 mg (0.11 mmol) of $NaBH_3CN$. After stirring for 2 h at 23 °C, 2 ml of 10% aqueous Na_2CO_3 was added, and the product was extracted into 4 x 1.5 ml of ethyl acetate. The organic phases were dried over $MgSO_4$ and evaporated to obtain 12.0 mg (95%) of **34** as a colorless glass: ^1H Nmr ($CDCl_3$) δ 5.65 (s), 5.16 (q, 1 H, J = 7 Hz), 3.92 (s, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.50 (s, 3 H), 3.32 (dm, 1 H, J = 7 Hz (d)), 3.21 (tt, 1 H, J = 5.5, 6.5 Hz), 2.44 (dd, 1 H, J = 6.5, 14 Hz), 2.09 (ddd, 1 H, J = 6, 8, 14 Hz), 1.88 (dm, 1 H, J = 14.5 Hz (d)), 1.80 (s, 3 H), 1.76 (dd, 1 H, J = 5, 14 Hz), 1.65 (d, 3 H, J = 6.5 Hz); ir (film) 2951, 1730, 1713, 1433, 1254, 1148, 733 cm^{-1}; ms (EI) *m/z* 355 (M^+, <1%), 324, 264 (100%), 233, 174, 131, 91, 59.

(*E*)-(2-Amino-10-ethylidene-4,5,6,9-tetrahydro-7-methyl-5,9-methanocycloocta[*d*]thiazol-1-yl)carbamic Acid Methyl Ester (36). A mixture of 200 mg (0.8 mmol) of **3**, 964 mg (8 mmol) of anhydrous $MgSO_4$, 334 μl (4 mmol) of pyrrolidine, and 4 ml of dry toluene was heated at 100 °C for 8 h in a resealable tube under argon. After cooling, the mixture was diluted with toluene and filtered, and the filtrate was concentrated. The residue was dissolved in dry methanol (1.5 ml), and 26.1 mg of sulfur (102 μmol of S_8) was added. After stirring for 15

min at 23 °C, 34.3 mg (816 μmol) of cyanamide was added, and the solution was stirred for 50 h at 23 °C under argon. Removal of the solvent and chromatography on silica gel with methanol/$CHCl_3$ 8:92 afforded 215 mg (88%) of **36** as yellowish prisms: mp 150-152 °C (from ethyl acetate/hexane); ^{1}H nmr ($CDCl_3$) δ 5.71 (m, 1 H), 5.23 (q, 1 H, *J* = 6.5 Hz), 5.06 (s, N*H*), 4.96 (br s, NH_2), 4.13 (d, 1 H, *J* = 6.5 Hz), 3.67 (s, 3 H), 3.11 (d, 1 H, *J* = 15.5 Hz), 2.83 (m, 2 H), 2.53 (d, 1 H, *J* = 17.5 Hz), 1.70 (d, 3 H, *J* = 6.5 Hz), 1.60 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 165.58, 142.01, 137.07, 135.32, 125.05, 123.19, 110.94, 56.20, 51.95, 46.94, 45.13, 32.70, 22.40, 13.36 (1 C not observed); ir (KBr) 3325, 1716, 1521, 1240, 734 cm^{-1}; ms *m/z* 305 (M$^+$, 20%), 258, 230 (100%), 215, 188, 171, 128; hrms calcd for $C_{15}H_{19}N_3O_2S$ 305.1198, found 305.1199.

(*E*)-2,5-Diamino-10-ethylidene-4,5,8,9-tetrahydro-7-methyl-5,9-methanocycloocta[*d*]thiazole (37). To a solution of 52 mg (0.17 mmol) of **36** in 5.5 ml of dry chloroform was added at rt 96 μl (0.68 mmol) of Me_3SiI, and the mixture was refluxed for 5.5 h under argon. After cooling and evaporation, the residue was dissolved in 5.5 ml of methanol, and the solution was refluxed for 15 h. The solvent was removed under vacuum, the residue was dissolved in 1 ml of dry dioxane, and 60 μl (0.68 mmol) of triflic acid was added. The solution was heated at 84 °C for 11 h. The solvent was evaporated, and the crude product was partitioned between 10% $NaHCO_3$ solution and ethyl acetate. Chromatography on silica gel with methanol/$CHCl_3$ 15:85 gave 36 mg (86%) of **37** as colorless prisms: mp 150-156 °C (from ethyl acetate/hexane 1.19), ^{1}H nmr ($CDCl_3$/CD_3OD) δ 5.42 (q, 1 H, *J* = 6.5 Hz), 5.23 (s, 1 H), 4.01 (d, 1 H, *J* = 4 Hz), 2.72 (d, 1 H, *J* = 15.5 Hz), 2.43 (d, 1 H, *J* = 15.5 Hz), 2.32 (m, 1 H), 1.98 (d, 1 H, *J* = 17 Hz), 1.67 (d, 3 H, *J* = 6.5 Hz), 1.56 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 166.41, 144.37, 141.31, 133.58, 130.09, 121.38, 111.30, 53.98, 42.65, 39.35, 32.04, 22.79, 12.55; ir (KBr) 3306, 3173, 1631, 1529, 1373, 754 cm^{-1}; ms *m/z* 247 (M$^+$, 100%), 232, 190, 172, 153, 134.

(*E*)-2,5-Diamino-10-ethylidene-4,5,6,9-tetrahydro-7-methyl-5,9-methanocycloocta[*d*]thiazole (38). To a solution of 120 mg (0.39 mmol) of **36** in 0.5 ml of dry HMPA was added at 23 °C under argon 5.2 ml (2.6 mmol) of a 0.5 M solution of *n*-PrLi in HMPA. The mixture was stirred at 38 °C for 24 h, then cooled to 0 °C and treated with water. After extraction with ethyl acetate, the organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with methanol/$CHCl_3$ 22:78 to afford 89 mg (93%) of **38** in 95% isomeric purity (remainder: **37**) as a white solid: mp 148-150 °C (from ethyl acetate/hexane 1:19); ^{1}H nmr ($CDCl_3$/CD_3OD) δ 5.65 (m, 1 H), 5.36 (q, 1 H, *J* = 6.5 Hz), 4.02 (d, 1 H, *J* = 6 Hz), 2 87 (d, 1 H, *J* = 16.5 Hz), 2.52-2.39 (m, 2 H), 2.07 (d, 1 H, *J* = 18 Hz), 1.65 (d, 3 H, *J* = 6.5 Hz), 1.50 (s, 3 H); ^{13}C nmr ($CDCl_3$) δ 166.38, 142.49, 141.88, 134.33, 125.90, 122.91, 110.40, 53.38, 50.11, 46.73, 32.75, 22.17, 12.94; ir (KBr) 3292, 3173, 1624, 1529, 754 cm^{-1}; ms *m/z* 247 (M$^+$, 30%), 232 (100%), 190, 172, 157, 134, 115.

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