# Studies toward the Total Synthesis of the Oxindole Alkaloid Gelsedine: An Efficient Allene-Terminated *N*-Acyliminium Ion Cyclization

Winfred G. Beyersbergen van Henegouwen and Henk Hiemstra*

*Laboratory of Organic Chemistry, Amsterdam Institute of Molecular Studies, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands*

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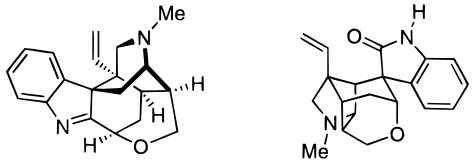
This paper reports the synthesis of the advanced intermediate **26** in a projected synthesis of enantiopure *ent*-gelsedine (**5**). The route starts from (*S*)-malic acid and features the creation of four new stereocenters with complete control of stereochemistry. The key step is a novel allene-terminated *N*-acyliminium ion cyclization that leads to the required 7-azabicyclo[4.2.1]nonane-4,8-dione skeleton. Additional functionalities including the C-8 ethyl and the C-9 hydroxymethyl are introduced in an efficient manner.

## Introduction

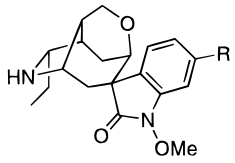
The three species of the plant genus *Gelsemium* (Loganiaceae) are a rich source of indole alkaloids with remarkably complex and diverse structures.[1] The most salient examples are the skeletons present in the parent compounds koumine (**1**), gelsemine (**2**), and gelsedine (**3**). Success in the area of total synthesis of these structures is only of relatively recent date, when Magnus and co-workers reported the first total synthesis of koumine in 1989.[2] More recently, a number of total syntheses of gelsemine were published by our group[3] and others.[4] This paper deals with a portion of our recent work toward the total synthesis of gelsedine. Our studies are motivated by the challenging molecular architecture of the *Gelsemium* alkaloids and by the interesting biological activity that some of these natural products display. In fact, extracts from *Gelsemium* species have a rich medicinal history, particularly in China.[1]



**1** (koumine)



**2** (gelsemine)



**3** (gelsedine, R = H)
**4** (gelsemicine, R = OMe)

Gelsedine (**3**) was isolated from Carolina jasmine (*Gelsemium sempervirens*) in 1953 by Schwarz and Marion[5] and was later found to occur also in *G. elegans*.[6] Its structure was elucidated by Wenkert and co-workers[7] in 1962 on the basis of a spectroscopic comparison with its 11-methoxy analogue gelsemicine (**4**). The structure of **4** was already determined in 1961 through X-ray crystallography by Przybylska and Marion.[8] In 1994, the first formal total synthesis of gelsedine starting from koumidine, an intermediate in Magnus' koumine synthesis,[2] was accomplished by Sakai et al.[9] Other studies aimed at a more direct total synthesis of gelsedine have been reported by three groups,[10] but a successful total synthesis has not yet appeared.

Our retrosynthetic analysis to gelsedine starting from malic acid is shown in Scheme 1. By using the inexpensive (*S*)-enantiomer as starting material, we realized that we would eventually arrive at *ent*-gelsedine (**5**), but this was preferred over a racemic synthesis. In analogy with our strategy to gelsemine,[3] we envisaged the closure of the tetrahydropyran ring via electrophile-induced etherification of **6** as a key step to complete the construction of the skeleton. Heck cyclization of the suitably protected amide **7** should lead to the oxindole **6**.[3,11] It is known that the stereochemistry of the Heck cyclization can be influenced by the choice of the catalyst.[3,12] Regioselective enolate formation from **8**, followed by its trapping as an enol triflate and Pd-catalyzed aminocarbonylation, should lead to anilide **7**.[13] The conversion of **9** to **8** depends on the stereoselective introduction of a two-carbon and a one-carbon fragment on C-8 and C-9, respectively. Treatment of **10** with acid will generate an *N*-acyliminium ion,

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1997.

(1) For reviews on *Gelsemium* alkaloids, see: (a) Liu, Z.-J.; Lu, R.-R. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, p 83. (b) Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. 8, p 93.

(2) Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220.

(3) Newcombe, N. J.; Fang, Y.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 767.

(4) (a) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765. (b) Kuzmich, D.; Wu, S. C.; Ha, D.-C.; Lee, C.-S.; Ramesh, S.; Atarashi, S.; Choi, J.-K.; Hart, D. J. *J. Am. Chem. Soc.* **1994**, *116*, 6943. (c) Fukuyama, T.; Gang, L. *J. Am. Chem. Soc.* **1996**, *118*, 7426. (d) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226.

(5) Schwarz, H.; Marion, L. *Can. J. Chem.* **1953**, *31*, 958.

(6) Yang, Y.-S.; Chen, Y.-W. *Acta Pharm. Sin.* **1983**, *18*, 104

(7) Wenkert, E.; Orr, J. C.; Garratt, S.; Hansen, J. H.; Wickberg, B.; Leicht, C. L. *J. Org. Chem.* **1962**, *27*, 4123.

(8) Przybylska, M.; Marion, L. *Can. J. Chem.* **1961**, *39*, 2124.

(9) Takayama, H.; Tominaga, Y.; Kitajama, M.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1994**, *59*, 4381.

(10) (a) Baldwin, S. W.; Doll, R. J. *Tetrahedron Lett.* **1979**, *35*, 3275. (b) Kende, A. S., Luzzio, M. J., Mendoza, J. S. *J. Org. Chem.* **1990**, *55*, 918. (c) Hamer, N. K. *J. Chem. Soc., Chem. Commun.* **1990**, 102.

(11) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(12) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859.

(13) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(14) Klaver, W. J.; Hiemstra, H.; Speckamp W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588.

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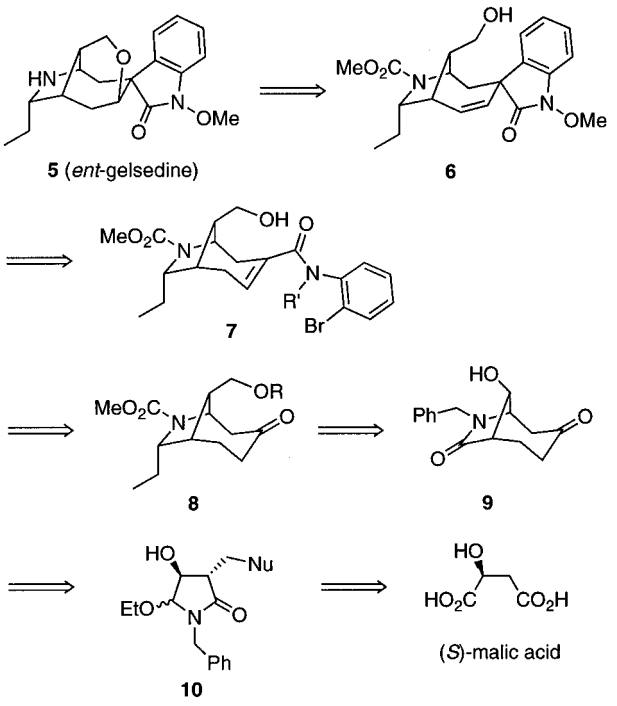
**Scheme 1**



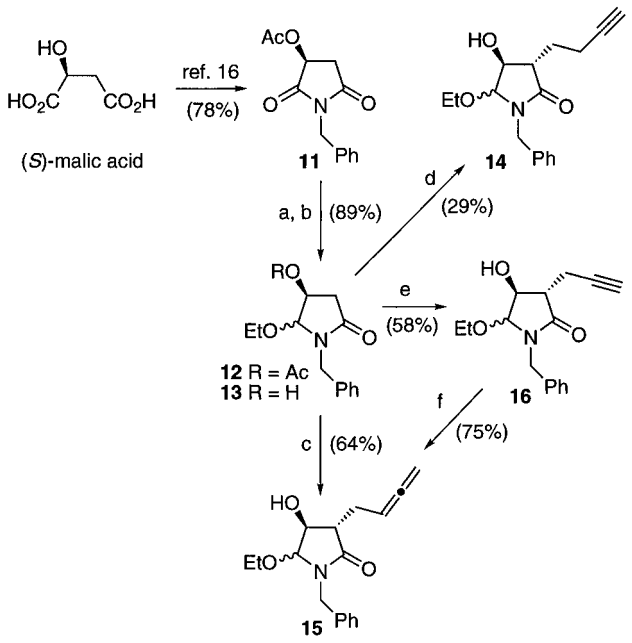

which was expected to cyclize on reaction with the proper $\pi$-nucleophile to give the bicyclic skeleton **9**. The early stages of this strategy bear resemblance to our total synthesis of the indole alkaloid peduncularine.[14]

In this paper, we report an efficient synthesis of enantiopure bicyclic ketone **8** starting from (*S*)-malic acid. Our approach features an efficient allene-terminated *N*-acyliminium cyclization.

## Results and Discussion

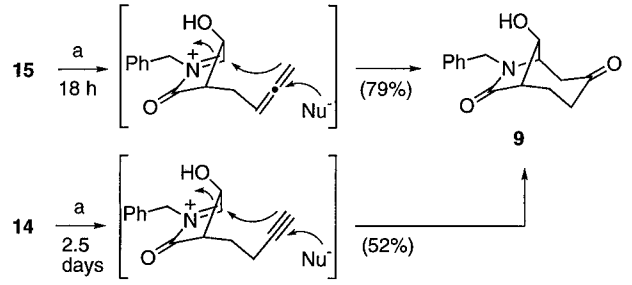
At the onset of our studies, we planned to apply an alkyne-terminated *N*-acyliminium ion cyclization as the key step to arrive at the 7-azabicyclo[4.2.1]nonane skeleton of ketone **9**. Precedent for this type of cyclization is available.[15] The required starting material **11** was synthesized from (*S*)-malic acid using a literature route (Scheme 2).[16] Regioselective reduction of **11** with $NaBH_4$, immediately followed by acidic ethanolysis, produced a mixture of acetate **12** and its deacetylated product **13**. Complete deacylation was effected by treatment of the crude mixture with $K_2CO_3$ in methanol, giving alcohol **13** as an 80:20 mixture of C-5 epimers. The crucial alkylation reaction of the dianion from **13** (generated by using 2.1 equiv of LDA) with 1-iodo-3-butyne at a reaction temperature of −117 °C gave the desired alkyne **14** in an unsatisfactory yield of 29%. Despite extensive experimentation this yield could not be improved, as higher temperatures probably gave increased levels of hydrogen iodide elimination from the alkylating agent. On the positive side, the alkylation at C-3 occurred exclusively *trans* with respect to the stereocenter at C-4.

**Scheme 2**[a]




[a] Conditions: (a) $NaBH_4$, EtOH, −15 °C, 1 h, then 1 M $H_2SO_4$ in EtOH, −25 °C → rt; (b) $K_2CO_3$, MeOH, rt, 1 h; (c) (1) LDA, THF, −78 °C, then −25 °C, 1 h; (2) 1-bromo-2,3-butadiene, −78 °C, 4 h, then rt, 18 h; (d) (1) LDA, THF, −78 °C, then −25 °C, 1 h; (2) 1-iodo-3-butyne, −117 °C, 6 h, then rt, 18 h; (e) (1) LDA, THF, −78 °C, then −25 °C, 1 h; (2) propargyl bromide, −78 °C, 4 h, then rt, 18 h; (f) CuI, *i*-$Pr_2NH$, $(CH_2O)_n$, 1,4-dioxane, reflux, 18 h.

**Scheme 3**[a]




[a] Conditions: (a) (1) $HCO_2H$, 85 °C; (2) 50% $NH_3$ in MeOH, rt, 1 h; $Nu^- = {}^-O_2CH$.

With the desired alkyne **14** in hand, its *N*-acyliminium cyclization was studied. This process required prolonged heating of **14** in formic acid for 60 h at 85 °C. The resulting product was directly deformylated with ammonia in methanol to give the expected ketone **9** as the only isolable product in 52% yield as a nicely crystalline solid (Scheme 3). The structure of **9** was proven through X-ray crystallography (Figure 1).

Both the low alkylation and the moderate cyclization yield described above led us to search for alternative ways to arrive at ketone **9**. It occurred to us that cationic cyclization of allene **15** should lead to the same ketone **9** (Scheme 3). There is one indication in the literature that

(15) (a) Racemic synthesis of a 7-azabicyclo[4.2.1]nonane system via *N*-acyliminium ion−alkyne cyclization: Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. Other racemic syntheses of these bicyclic systems: (b) Malpass, J. R. *J. Chem. Soc., Chem. Commun.* **1972**, 1246. (c) Newman, H.; Fields, T. L. *Tetrahedron* **1972**, *28*, 4051. (d) Mondon, A.; Aumann, G.; Oelrich, E. *Chem. Ber.* **1972**, *105*, 2025. (e) Coates, J. E.; Casy, A. F. *J. Org. Chem.* **1974**, *39*, 3044. (f) Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 3805. (g) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1988**, *44*, 6729. Enantiopure synthesis of this bicyclic system: (h) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 1581.

(16) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.

(17) (a) Schoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1980**, *36*, 143. (b) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 3289. (c) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3807. (d) Nossin, P. M. M. Ph.D. Thesis, University of Amsterdam, 1983.

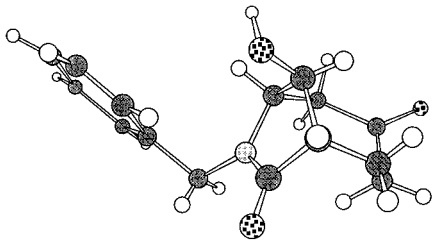
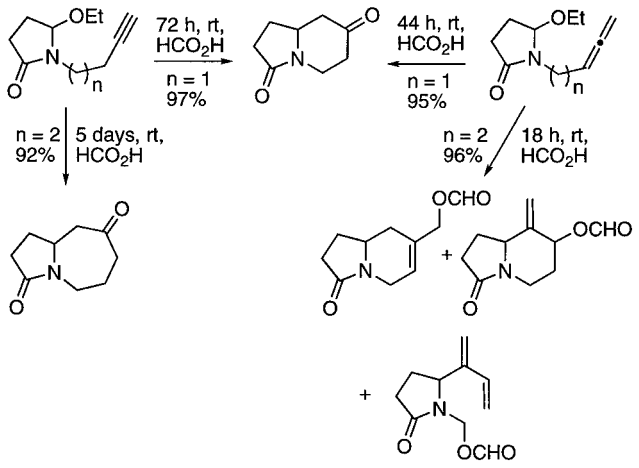


**Figure 1.** Molecular structure of **9** determined by X-ray crystallography.

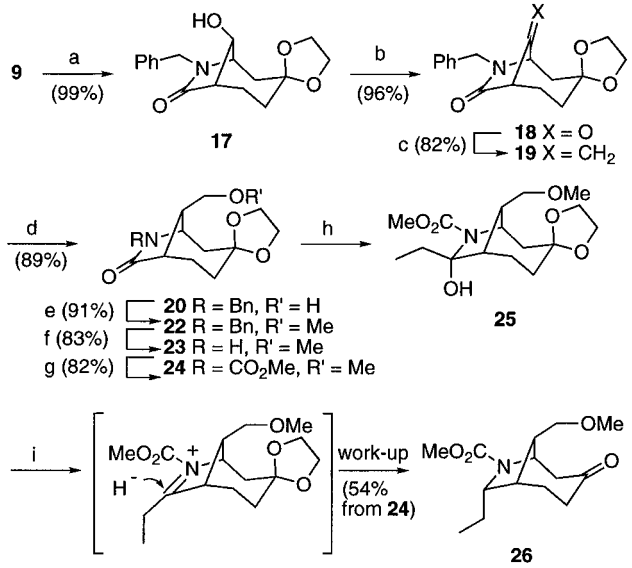
**Scheme 4**




an allene may be somewhat more reactive than an alkyne in *N*-acyliminium cyclization processes leading to the same ketone, although this particular example pertains to six-membered ring formation (Scheme 4).[17,18] For the synthesis of **15**, the dianion of **13** was first alkylated with propargyl bromide the give alkyne **16** in 58% yield. The latter alkyne was then subjected to a Crabbé homologation[19] to provide the desired allene **15** in 75% yield. A more direct route to **15** involved the alkylation of **13** with 1-bromo-2,3-butadiene[20] to furnish the allene in a satisfactory 64% yield. Moreover, these alkylations to **15** and **16** could be conveniently carried out at temperatures not lower than −78 °C and proceeded with complete trans selectivity with respect to the C-4 stereocenter.

The key cationic cyclization of allene **15** proceeded smoothly at 85 °C in formic acid to furnish in only 18 h 79% of ketone **9** after subsequent deformylation (Scheme 3). Thus, we have now developed a fairly direct synthesis of the enantiopure bicyclic ketone **9** via a novel and efficient *N*-acyliminium allene cyclization. It is interesting to note here that the homologous alkyne and allene of the literature system (Scheme 4) behave in a completely different fashion.[17] Whereas the alkyne cleanly led to the expected seven-membered ring ketone, the allene gave a mixture containing no seven-membered ring products. The geometry of the bicyclic transition state leading to **9** clearly plays a crucial role, preventing

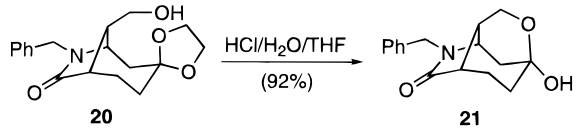
**Scheme 5**[a]




[a] Conditions: (a) $HOCH_2CH_2OH$, *p*-TsOH, reflux; (b) (1) $(ClCO)_2$, DMSO, $CH_2Cl_2$, −78 °C, 2 h; (2) $Et_3N$, rt, 15 min; (c) $Ph_3PMeBr$, *n*-BuLi, THF, 0 °C, then **18**, reflux, 18 h; (d) $BH_3{\cdot}SMe_2$, 0 °C → rt, 2 h, then $NaOH/H_2O_2$; (e) NaH, MeI, THF, rt, 18 h; (f) $Na/NH_3$, THF, −78 °C; (g) NaH, $ClCO_2Me$, THF, rt, 18 h; (h) EtMgCl, THF, −78 °C, 0.5 h; (i) $CF_3CO_2H$, $Et_3SiH$, $CH_2Cl_2$, 0 °C, 2 h, then rt, 1 h.

the internal double bond of the allene from participating in the $\pi$-cyclization process.

With a convenient access to ketone **9** secured, the further steps of our projected route to gelsedine were investigated. To introduce the required hydroxymethyl functionality, ketone **9** was protected as a dioxolane and then subjected to Swern oxidation affording ketone **18** (Scheme 5). Wittig olefination to **19** and subsequent hydroboration with the borane dimethyl sulfide complex and oxidative workup gave the desired alcohol **20** with complete stereoselectivity in the desired sense. Its stereochemistry was proven by hydrolysis of the dioxolane in **20**, which gave hemiacetal **21** in quantitative yield.




The hydroxyl group in **20** was then protected provisionally as a methyl ether to study the introduction of the C-8 ethyl substituent. The carbonyl group in *N*-benzyllactam **22** was unreactive toward ethylmagnesium chloride under several different conditions, so that activation of the carbonyl toward nucleophilic addition was required. Therefore, **22** was debenzylated by treatment with sodium in ammonia, and the product **23** was subsequently treated with methyl chloroformate to give the desired carbamate **24**. As expected, **24** smoothly reacted with ethylmagnesium chloride, even at −78 °C. Although the product, hemiaminal **25**, was stable at room temperature, its purification on silica gel gave partial five-membered ring-opening to the corresponding ketone. Hence, the crude product was immediately treated with trifluoroacetic acid, giving the *N*-acyliminium ion, which was reduced in situ with triethylsilane to produce carbamate **26** as a single stereoisomer.[21] As a bonus, the

(18) For intermolecular reactions of *N*-acyliminium ions with allenes, see: (a) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (b) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1988**, *29*, 4257.

(19) Crabbé, P.; Fillion, H.; Andre, K.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1979**, 859.

(20) Pornet, J.; Randrianoelina B.; Miginiac, L. *J. Organomet. Chem.* **1979**, *174*, 1.

(21) Reduction with $Et_3SiH/BF_3{\cdot}OEt_2$: Dijkink, J.; Eriksen, K.; Goubitz, K.; Van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron: Asymmetry* **1996**, *7*, 515.

dioxolane was hydrolyzed during the aqueous workup. The stereochemistry of **26** was proven by NOE measurements (a NOE of 10.4% was observed between H-8 and H-9).

In conclusion, we have prepared in an efficient way an advanced synthetic intermediate in our projected synthesis of enantiopure *ent*-gelsedine. Four new stereocenters have been created with complete control from only one in the starting material (*S*)-malic acid. A novel *N*-acyliminium allene cyclization served to arrive at the required 7-azabicyclo[4.2.1]nonane-4,8-dione skeleton. The additional functionalities including the C-8 ethyl and the C-9 hydroxymethyl were introduced with complete stereocontrol. Remaining challenges include the stereoselective introduction of the oxindole moiety and closure of the tetrahydropyran ring, which we will report on in due course.

## Experimental Section

**General Information.** All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry $N_2$ atmosphere. Unless otherwise noted, reagents were added by syringe. Column chromatography was performed with Merck 60 (230−400 mesh) silica gel using the procedure of Still.[22] Thin-layer chromatography (TLC) was performed with Merck F-254 silica gel plastic sheets. All starting materials were obtained from commercial suppliers and used without further purification. THF and ether were distilled from sodium/benzophenone immediately prior to use. Dichloromethane ($CH_2Cl_2$), benzene, triethylamine, and diisopropylamine were distilled from $CaH_2$ immediately prior to use. Dimethyl sulfoxide (DMSO) was dried and stored over 4 Å molecular sieves. IR spectra ($cm^{-1}$) were measured as thin films on NaCl plates unless otherwise noted. $^1H$ NMR and $^{13}C$ NMR spectra were measured as solutions in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal $CHCl_3$ (7.26 ppm). Mass spectra were measured using electron impact (EI) mass spectrometry, unless otherwise noted. Elemental analyses were performed at the University of Amsterdam by J. Dijkink.

**(4*S*,5*R*)-1-Benzyl-5-ethoxy-4-hydroxy-2-pyrrolidinone and (4*S*,5*S*) Epimer (13).** To a stirred solution of **11**[16] (32.6 g, 0.132 mol) in EtOH (850 mL) at −35 °C was added $NaBH_4$ (25.00 g, 0.661 mol). An ethanolic solution of $H_2SO_4$ (ca. 3.5 mL, 4 M) was added dropwise at −35 °C to catalyze the reduction. After the reaction mixture was stirred for 1 h at −15 °C, it was cooled to −50 °C, and an ethanolic solution of $H_2SO_4$ (ca. 585 mL, 1 M) was added over a period of 30 min (the temperature was maintained below −25 °C). After the reaction mixture was stirred for 18 h at rt, it was poured onto saturated aqueous $NaHCO_3$ (400 mL), $H_2O$ was added (1200 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (4 × 400 mL). The combined organic layers were washed with $H_2O$ (4 × 600 mL), dried ($MgSO_4$), and concentrated in vacuo to give a colorless oil of a mixture of **12** and **13**. To complete the deacetylation, $K_2CO_3$ (3.65 g, 0.0264 mol) was added to a solution of this oil in MeOH (50 mL). After the solution was stirred for 1 h at rt, it was poured onto saturated aqueous $NH_4Cl$ (50 mL). Extraction with $CH_2Cl_2$ (3 × 50 mL), followed by drying ($MgSO_4$) and concentration of the combined organic layers in vacuo, gave pure **13** (27.64 g, 89%) as a yellowish oil (80:20 mixture of epimers). Major isomer: $R_f$ 0.36 ($CH_2Cl_2$/acetone 2:1); IR 3393, 2929, 1682; $^1H$ NMR (400 MHz) 1.17 (t, $J$ = 7.0 Hz, 3H), 2.02 (br, 1H), 2.33 (dd, $J$ = 1.4, 17.6 Hz, 1H), 2.89 (ddd, $J$ = 0.9, 6.3, 17.6 Hz, 1H), 3.45 (m, 2H), 3.53 (m, 2H), 4.06 (d, $J$ = 15.0 Hz, 1H), 4.24 (t, $J$ = 4.7 Hz, 1H), 4.97 (d, $J$ = 15.0 Hz, 1H), 7.29 (m, 5H); $^{13}C$ NMR (100 MHz) 15.0, 38.8, 43.7, 53.3, 68.6, 95.0, 127.3, 127.8, 128.5, 135.8; HRMS calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1192.

**General Procedure for Alkylation of 12: (3*S*,4*S*,5*R*)-1-Benzyl-5-ethoxy-4-hydroxy-3-(but-3-ynyl)-2-pyrrolidinone and (3*S*,4*S*,5*S*) Epimer (14).** To a mechanically stirred solution of diisopropylamine (11.2 mL, 80.36 mmol) in THF (100 mL) was added under nitrogen at −78 °C a 1.6 M solution of *n*-BuLi in hexane (50.2 mL, 80.36 mmol). After the mixture was stirred for 15 min at −78 °C, a solution of the epimeric mixture **13** (9.00 g, 38.25 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 1 h at −20 °C and then cooled to −117 °C. A solution of 1-iodobutyne (16.74 g, 93.0 mmol) in THF (10.0 mL) was slowly added. The reaction mixture was stirred for 6 h at −117 °C, allowed to warm slowly, stirred for 18 h at rt, and then poured onto saturated aqueous $NH_4Cl$ (100 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (first $CH_2Cl_2$/acetone 6:1, then $CH_2Cl_2$/acetone 2:1 to recover unreacted **13**) to give **14** (3.19 g, 29%) as a light-yellow oil. Major isomer: $R_f$ 0.44 ($CH_2Cl_2$/acetone 6:1); IR 3290, 2928, 1681; $^1H$ NMR (400 MHz) 1.18 (t, $J$ = 7.6 Hz, 3H), 1.74 (m, 1H), 2.04 (t, $J$ = 2.6 Hz, 1H), 2.16 (m, 1H), 2.46 (m, 2H), 2.76 (br, 1H), 3.52 (m, 2H), 4.02 (d, $J$ = 14.8 Hz, 1H), 4.02 (s, 1H), 4.47 (d, $J$ = 2.3 Hz, 1H), 4.94 (d, $J$ = 14.8 Hz, 1H), 7.28 (m, 5H); $^{13}C$ NMR (100 MHz) 15.3, 16.7, 28.5, 43.4, 49.8, 64.1, 69.4, 75.8, 83.8, 93.6, 127.8, 128.1, 128.6, 135.9, 173.9; HRMS calcd for $C_{17}H_{21}NO_3$ 287.1521, found 287.1592.

**(3*S*,4*S*,5*R*)-1-Benzyl-5-ethoxy-4-hydroxy-3-(buta-2,3-dienyl)-2-pyrrolidinone and (3*S*,4*S*,5*S*) Epimer 15.** Alkylation of **13** (1.60 g, 6.8 mmol) with 1-bromo-2,3-butadiene (1.50 g, 11.3 mmol) (4 h at −78 °C, then 18 h at rt) gave after chromatography ($CH_2Cl_2$/acetone 6:1) **15** (1.26 g, 64%) as a light-yellow oil. Major isomer: $R_f$ 0.47 ($CH_2Cl_2$/acetone 6:1); IR 3394, 1956, 1678; $^1H$ NMR (400 MHz) 1.16 (t, $J$ = 7.0 Hz, 3H), 2.25 (m, 1H), 2.46 (m, 1H), 2.55 (br, 1H), 2.60 (m, 1H), 3.50 (m, 2H), 4.01 (s, 1H), 4.04 (d, $J$ = 15.0 Hz, 1H), 4.45 (d, $J$ = 1.5 Hz, 1H), 4.72 (m, 2H), 5.19 (q, $J$ = 6.7 Hz, 1H), 4.92 (d, $J$ = 14.9 Hz, 1H), 7.26 (m, 5H); $^{13}C$ NMR (100 MHz) 15.3, 28.4, 43.5, 50.5, 63.9, 74.6, 75.7, 87.4, 93.7, 127.5, 128.1, 128.1, 128.2, 128.6, 136.0, 174.0, 209.1; HRMS calcd for $C_{17}H_{21}NO_3$ 287.1521, found 287.1515.

**(3*S*,4*S*,5*R*)-1-Benzyl-5-ethoxy-4-hydroxy-3-(prop-2-ynyl)-2-pyrrolidinone and (3*S*,4*S*,5*S*) Epimer (16).** Alkylation of **13** (11.60 g, 49.3 mmol) with 80% propargyl bromide in toluene (8.28 mL, 74.3 mmol) (4 h at −78 °C, then 18 h at rt) gave after chromatography ($CH_2Cl_2$/acetone 6:1) **16** (7.82 g, 58%) as a light-yellow oil. Major isomer: $R_f$ 0.71 ($CH_2Cl_2$/acetone 2:1); IR 3292, 2929, 1680; $^1H$ NMR (400 MHz) 1.15 (t, $J$ = 7.0 Hz, 3 H), 2.01 (t, $J$ = 2.2 Hz, 1 H), 2.52 (m, 2H), 2.68 (d, $J$ = 15 Hz, 1H), 3.51 (m, 2H), 3.99 (br, 1H), 4.01 (d, $J$ = 14.9 Hz, 1H), 4.18 (s, 1H), 4.49 (d, $J$ = 2.6 Hz, 1H), 4.87 (d, $J$ = 14.9 Hz, 1H), 7.24 (m, 5H); $^{13}C$ NMR (100 MHz) 15.2, 18.2, 43.3, 49.0, 63.9, 70.5, 74.6, 80.8, 93.2, 127.4, 128.0, 128.5, 128.6, 128.6, 135.6, 172.3; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1375.

**(3*S*,4*S*,5*R*)-1-Benzyl-5-ethoxy-4-hydroxy-3-(buta-2,3-dienyl)-2-pyrrolidinone and (3*S*,4*S*,5*S*) Epimer (15).** To a stirred solution of **16** (7.73 g, 28.3 mmol) in 1,4-dioxane (100 mL) were added copper(I) iodide (2.69 g, 14.1 mmol), diisopropylamine (7.95 mL, 56.6 mmol), and paraformaldehyde (1.27 g, 70.1 mmol). After the reaction mixture was stirred for 18 h at reflux, it was cooled to rt and filtered over Celite. The 1,4-dioxane was evaporated, and the residue was taken up in $CH_2Cl_2$ (250 mL). The organic layer was washed with a 10% solution of ammonia in brine (2 × 100 mL), water (pH = 2, 2 × 100 mL), water (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/acetone 6:1) to give **15** (6.07 g, 75%) as a light-yellow oil.

**(1*S*,6*R*,9*S*)-7-Benzyl-9-hydroxy-7-azabicyclo[4.2.1]nonane-4,8-dione (9).** A solution of **14** (3.19 g, 11.10 mmol) in $HCO_2H$ (55 mL) was stirred at 85 °C for 2.5 days and then concentrated in vacuo. The residue was dissolved in a 50% methanolic $NH_3$ solution (50 mL). After this solution was stirred for 1 h at rt, the MeOH was evaporated and the residue was chromatographed ($CH_2Cl_2$/acetone 1:1) to give **9** as a white crystalline solid, which was recrystallized from EtOAC to give

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

white needles (1.49 g, 52%): mp 208−210 °C; $[\alpha]^{20}_D$ +16.9 (*c* 0.99, $CHCl_3$); $R_f$ 0.40 ($CH_2Cl_2$/acetone 1:1); IR 3403, 1695, 1652; $^1$H NMR (400 MHz) 1.76 (m, 1H), 2.17 (m, 1H), 2.21 (br, 1H), 2.37 (dd, *J* = 4.6, 8.9 Hz, 2H), 2.44 (dd, *J* = 4.8, 16.1 Hz, 1H), 2.54 (dd, *J* = 2.1, 16.1 Hz, 1H), 2.75 (dd, *J* = 3.3, 4.5 Hz, 2H), 3.63 (dd, *J* = 2.1, 4.8 Hz, 1H), 3.78 (s, 1H), 4.26 (d, *J* = 15.1 Hz, 1H), 4.95 (d, *J* = 15.1 Hz, 1H), 7.35 (m, 5H); $^{13}$C NMR (100 MHz) 24.8, 39.9, 44.1, 44.4, 51.2, 60.6, 74.7, 128.0, 128.1, 128.9, 135.7, 174.3, 209.1; HRMS calcd for $C_{15}H_{17}NO_3$ 259.1208, found 259.1207. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.41; H, 6.86; N, 5.20. An X-ray crystal structure was obtained: monoclinic, $P2_1$, *a* = 7.0609(6) Å, *b* = 9.7810(7) Å, *c* = 9.758(1) Å, *V* = 667.3(1) Å$^3$, *Z* = 2, $D_x$ = 1.29 g cm$^{-3}$, $\lambda$(Cu K$\alpha$) = 1.5418 Å, $\mu$(Cu K$\alpha$) = 6.95 cm$^{-1}$, *F* (000) = 276, −20 °C. Final *R* = 0.042 for 1297 observed reflections.

**(1*S*,6*R*,9*S*)-7-Benzyl-4,4-(ethylenedioxy)-9-hydroxy-7-azabicyclo[4.2.1]nonan-8-one (17).** A solution of **9** (1.59 g, 6.13 mmol), ethylene glycol (1.03 mL, 18.38 mmol), and *p*-toluenesulfonic acid monohydrate (0.175 g, 0.919 mmol) in benzene (12 mL) was refluxed, and benzene (4 × 8 mL) was distilled off. The reaction mixture was cooled and then poured onto saturated aqueous $NaHCO_3$ (40 mL) and was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. This gave pure **17** (1.84 g, 99%) as a white solid, which was used without further purification: mp 178−180 °C; $[\alpha]^{20}_D$ +47.0; $R_f$ 0.50 (acetone 1:1); IR 3406, 2951, 1674; $^1$H NMR (400 MHz) 1.64 (m, 2H), 1.80 (dd, *J* = 5.2, 15.2 Hz, 1H), 1.91 (m, 3H), 2.30 (br, 1H), 2.61 (t, *J* = 4.1 Hz, 1H), 3.44 (dd, *J* = 1.4, 5.0 Hz, 1H), 3.58 (m, 4H), 3.95 (d, *J* = 15.3 Hz, 1H), 4.41 (s, 1H), 5.05 (d, *J* = 15.3 Hz, 1H), 7.29 (m, 5H); $^{13}$C NMR (100 MHz) 22.6, 32.3, 37.4, 43.4, 51.2, 61.9, 63.8, 64.3, 71.6, 110.3, 127.5, 127.9, 128.7, 136.01, 175.5; HRMS calcd for $C_{17}H_{21}NO_4$ 303.1470, found 303.1468.

**(1*S*,6*R*)-7-Benzyl-4,4-(ethylenedioxy)-7-azabicyclo[4.2.1]-nonane-8,9-dione (18).** To a stirred solution of oxalyl chloride (0.83 mL, 9.49 mmol) in $CH_2Cl_2$ (10 mL) was added DMSO (1.44 mL, 20.28 mmol) at −78 °C. After the reaction mixture was stirred for 5 min, **17** (1.81 g, 5.96 mmol) was added, and the reaction mixture was stirred for 2 h at −78 °C. Then $Et_3N$ (6.21 mL, 44.62 mmol) was added, and the reaction mixture was allowed to warm to rt, stirred at this temperature for 15 min, and poured onto saturated aqueous $NH_4Cl$ (40 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (EtOAc) to give **18** (0.172 g, 96%) as a colorless oil: $[\alpha]^{20}_D$ +48.2 (*c* 0.89, $CHCl_3$); $R_f$ 0.47 (EtOAc); IR 3018, 1776, 1692; $^1$H NMR (400 MHz) 1.75 (m, 1H), 1.88 (m, 2H), 2.09 (m, 3H), 3.01 (dd, *J* = 3.5, 6.0 Hz, 1H), 3.73 (dd, *J* = 2.6, 4.4 Hz, 1H), 3.90 (m, 4H), 4.00 (d, *J* = 14.9 Hz, 1H), 5.24 (d, *J* = 14.9 Hz, 1H), 7.29 (m, 5H); $^{13}$C NMR (100 MHz) 24.2, 33.1, 35.9, 43.3, 51.4, 61.6, 64.1, 64.7, 109.3, 128.02, 128.3, 128.9, 135.0, 171.5, 206.0; HRMS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1301.

**(1*S*,6*R*)-7-Benzyl-4,4-(ethylenedioxy)-9-methylene-7-azabicyclo[4.2.1]nonan-8-one (19).** To a stirred solution of methyltriphenylphosphonium bromide (3.24 g, 9.07 mmol) in THF (25 mL) was added at 0 °C a 1.6 M solution of *n*-BuLi in hexane (5.39 mL, 8.36 mmol). After 25 min, a solution of **18** (1.66 g, 5.56 mmol) in THF (5 mL) was added. The reaction mixture was refluxed for 18 h and then poured onto saturated aqueous $NH_4Cl$ (40 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/acetone 4:1) to give **19** (1.36 g, 82%) as a white solid: mp 138−140 °C; $[\alpha]^{20}_D$ +17.3 (*c* 1.00, $CHCl_3$); $R_f$ 0.49 ($CH_2Cl_2$/acetone 4:1); IR 3009, 1693, 1672; $^1$H NMR (400 MHz) 1.75 (m, 2H), 1.87 (m, 2H), 2.02 (m, 1H), 2.18 (ddd, *J* = 1.0, 2.7, 14.7 Hz, 1H), 3.14 (dd, *J* = 0.9, 6.6 Hz, 1H), 3.87 (m, 6H), 4.98 (s, 2H), 5.13 (d, *J* = 15.3 Hz, 1H), 7.27 (m, 5H); $^{13}$C NMR (100 MHz) 25.4, 32.9, 40.2, 43.4, 47.3, 58.6, 63.2, 64.6, 108.2, 110.2, 127.5, 128.0, 128.7, 136.2, 144.9, 175.9; HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1532. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.69; H, 6.92; N, 4.69.

**(1*S*,6*R*,9*R*)-7-Benzyl-4,4-(ethylenedioxy)-9-(hydroxymethylene)-7-azabicyclo[4.2.1]nonan-8-one (20).** To $BH_3$·$Me_2S$ (2.80 mL of a 1 M solution in THF, 2.80 mmol) was added at 0 °C a solution of **19** (1.25 g, 4.16 mmol) in THF (3 mL). After being stirred for 2 h at rt, the solution was cooled to 0 °C and subsequently treated with 3 M aqueous NaOH (5.60 mL) and 35% aqueous $H_2O_2$ (2.40 mL). The resulting solution was stirred for 1 h at rt and then poured onto water (40 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/acetone 1:1) to give **20** (1.17 g, 89%) as a colorless oil: $[\alpha]^{20}_D$ +73.4 (*c* 1.01, $CHCl_3$); $R_f$ 0.33 ($CH_2Cl_2$/acetone 1:1); IR 3010, 1679; $^1$H NMR (400 MHz) 1.73 (m, 3H), 1.90 (m, 2H), 2.29 (dd, *J* = 2.9, 16.1 Hz, 1H), 2.60 (m, 1H), 2.69 (m, 1H), 3.54 (dt, *J* = 3.2, 6.7 Hz, 1H), 3.90 (m, 5H), 4.09 (m, 2H), 5.16 (d, *J* = 15.2 Hz, 1H), 7.27 (m, 5H); $^{13}$C NMR (100 MHz) 20.5, 32.9, 37.8, 42.9, 43.2, 44.6, 54.9, 59.0, 63.7, 64.1, 110.7, 127.3, 127.8, 128.5, 136.2, 176.2; HRMS calcd for $C_{18}H_{23}NO_4$ 317.1627, observed 317.1627.

**(1*S*,6*R*,9*R*)-6-Benzyl-1-hydroxy-10-oxa-6-azatricyclo-[5.3.1.0$^{4,8}$]decan-5-one (21).** A solution of **20** (0.040 g, 0.13 mmol) in THF/2 M HCl (1:1, 0.50 mL) was stirred for 4 h and then poured onto saturated aqueous $NaHCO_3$ (10 mL) and was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. This gave pure **21** (0.032 g, 92%) as a colorless oil: $[\alpha]^{20}_D$ +72.9 (*c* 1.38, $CHCl_3$); $R_f$ 0.32 ($CH_2Cl_2$/acetone 1:1); IR 3018, 2934, 1677; $^1$H NMR (400 MHz) 1.95 (m, 5H), 2.51 (t, *J* = 8.3 Hz, 1H), 2.55 (s, 1H), 2.80 (m, 1H), 3.75 (t, *J* = 7.4 Hz, 1H), 4.02 (m, 2H), 4.12 (dd, *J* = 1.8, 11.3 Hz), 5.00 (d, *J* = 14.9 Hz, 1H), 7.30 (m, 5H); $^{13}$C NMR (100 MHz) 23.1, 34.8, 38.3, 39.7, 43.6, 44.9, 52.8, 62.3, 97.1, 127.8, 128.2, 128.9, 136.2, 176.3; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, observed 273.1380.

**(1*S*,6*R*,9*R*)-7-Benzyl-4,4-(ethylenedioxy)-9-(methoxymethylene-)7-azabicyclo[4.2.1]nonan-8-one (22).** To a stirred solution of **20** (0.71 g, 2.29 mmol) in THF (5 mL) was added 60% NaH in mineral oil (0.28 g, 6.89 mmol) at rt. After the mixture was stirred for 0.5 h, methyl iodide (0.43 mL, 6.89 mmol) was added. The solution was stirred for 18 h and then poured onto saturated aqueous $NH_4Cl$ (15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/acetone 2:1) to give **22** (0.69 g, 91%) as a colorless oil: $[\alpha]^{20}_D$ +67.6 (*c* 1.00, $CHCl_3$); $R_f$ 0.49 ($CH_2Cl_2$/acetone 2:1); IR 3005, 2931, 1678; $^1$H NMR (400 MHz) 1.69 (m, 3H), 1.85 (m, 2H), 2.23 (dd, *J* = 3.0, 16.1 Hz, 1H), 2.62 (m, 2H), 3.28 (s, 3H), 3.47 (m, 1H), 3.67 (m, 1H), 3.85 (m, 6H), 5.11 (d, *J* = 15.2 Hz, 1H), 7.23 (m, 5H); $^{13}$C NMR (100 MHz) 20.6, 33.1, 37.8, 42.2, 42.9, 43.4, 55.1, 58.8, 64.0, 64.1, 68.9, 110.8, 127.4, 127.8, 128.6, 136.3, 176.3; HRMS calcd for $C_{19}H_{25}NO_4$ 331.1783, found 331.1766.

**(1*S*,6*R*,9*R*)-4,4-(Ethylenedioxy)-9-(methoxymethylene)-7-azabicyclo[4.2.1]nonan-8-one (23).** To a deep blue solution of sodium (0.174 g, 7.57 mmol) in condensed ammonia (25 mL) was added **22** (0.683 g, 2.06 mmol) in THF (5 mL) at −78 °C. The solution was stirred for 15 min at −78 °C, and then $NH_4Cl$ (0.440 g, 8.22 mmol) was added. The ammonia was allowed to evaporate slowly at rt by passing a stream of nitrogen over the solution. The THF was evaporated in vacuo, the residue was taken up in warm $CH_2Cl_2$ (40 mL) and filtered, and the solids were washed with warm $CH_2Cl_2$ (20 mL). The filtrate was concentrated in vacuo to give **23** (0.410 g, 83%) as a white crystalline solid: mp 145−146.5 °C; $[\alpha]^{20}_D$ +49.8 (*c* 0.99, $CHCl_3$); $R_f$ 0.53 (acetone); IR 3295, 2943, 1704, 1676; $^1$H NMR (400 MHz) 1.66 (m, 2H), 1.78 (m, 2H), 2.00 (dq, *J* = 3.5, 16.0 Hz, 2H), 2.45 (m, 1H), 2.77 (m, 1H), 2.86 (s, 3H), 3.78 (m, 7H), 6.98 (s, 1H); $^{13}$C NMR (100 MHz) 20.2, 32.9, 42.5, 42.9, 43.4, 52.9, 58.7, 63.7, 64.1, 68.9, 111.0, 179.5; HRMS calcd for $C_{12}H_{18}NO_4$ 241.1314, found 241.1314. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.94; H, 8.16; N, 5.69.

**(1*S*,6*R*,9*R*)-4,4-(Ethylenedioxy)-7-(methoxycarbonyl)-9-(methoxymethylene)-7-azabicyclo[4.2.1]nonan-8-one (24).** To a stirred solution of **23** (0.200 g, 0.829 mmol) in THF (3 mL) were added 60% NaH in mineral oil (0.133 g, 3.32

mmol) and methyl chloroformate (0.255 mL, 3.32 mmol) at rt. The solution was stirred for 18 h and then poured onto saturated aqueous $NH_4Cl$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/acetone 3:1) to give **24** (0.205 g, 82%) as a colorless oil: $[\alpha]^{20}_D$ +4.3 (*c* 1.01, $CHCl_3$); $R_f$ 0.52 ($CH_2Cl_2$/acetone 3:1); IR 2954, 1790, 1716; $^1$H NMR (400 MHz) 1.77 (m, 3H), 1.86 (m, 1H), 1.95 (dd, *J* = 3.2, 16.0 Hz, 1H), 2.48 (dd, *J* = 3.6, 7.2 Hz, 1H), 2.72 (m, 2H), 3.33 (s, 3H), 3.65 (m, 2H), 3.82 (m, 9H), 4.36 (quintet, *J* = 3.4 Hz, 1H); $^{13}$C NMR (100 MHz) 20.8, 33.5, 38.5, 40.7, 44.8, 53.4, 56.9, 58.9, 63.9, 64.4, 68.7, 110.3, 151.7, 175.9; HRMS calcd for $C_{14}H_{21}NO_6$ 299.1369, found 299.1358.

**(1*S*,6*R*,8*S*,9*R*)-8-Ethyl-7-(methoxycarbonyl)-9-(methoxymethylene)-7-azabicyclo[4.2.1]nonan-4-one (26).** Ethylmagnesium chloride (0.652 mL of a 2 M solution in THF, 1.30 mmol) was added to a solution of **24** (0.195 g, 0.651 mmol) in THF (4 mL) at −78 °C. After the solution was stirred for 0.5 h at −78 °C, saturated aqueous $NH_4Cl$ (1 mL) was added. The solution was allowed to warm to rt and then poured onto more saturated aqueous $NH_4Cl$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue (0.197 g) was not purified but directly used in the following reaction. To a solution of the residue in $CH_2Cl_2$ (1.20 mL) was added trifluoroacetic acid (0.300 mL, 3.91 mmol) at 0 °C and was stirred for 20 min at 0 °C. Then triethylsilane (0.416 mL, 2.60 mmol) was added. After the solution was stirred for 2 h at 0 °C and 1 h at rt, the solution was poured onto saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (EtOAc/hexanes 3:1) to give **26** (0.095 g, 54%) as a colorless oil: $[\alpha]^{20}_D$ +32.2 (*c* 1.01, $CHCl_3$); $R_f$ 0.44 (EtOAc/hexanes 3:1); IR 3021, 2955, 1691; $^1$H NMR (400 MHz) 0.96 (t, *J* = 7.4 Hz, 3H), 1.55 (m, 3H), 1.84 (dq, *J* = 4.3, 15.2 Hz, 1H), 2.42 (m, 2H), 2.50 (m, 1H), 2.60 (m, 1H), 2.91 (m, 2H), 3.32 (m, 5H), 3.58 (m, 1H), 3.71 (s, 3H), 4.18 (s, 1H); $^{13}$C NMR (100 MHz) 11.7, 19.9, 20.7, 38.3, 41.8, 44.5, 46.2, 52.2, 56.2, 59.2, 65.0, 69.3, 157.3, 212.6; HRMS calcd for $C_{14}H_{28}NO_4$ 269.1627, found 269.1638.

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**Supporting Information Available:** $^1$H NMR spectra of compounds **9**, **13**−**24**, and **26** and X-ray data of compound **9** (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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