JOC*Note*

Enantioselective Synthesis of Bicyclo[6.1.0]nonane-9-carboxylic Acids via Me_2AlOTf-Promoted Intramolecular Friedel−Crafts Alkylation of Arenes with the γ-Lactone Moiety of 3-Oxabicyclo[3.1.0]hexan-2-ones

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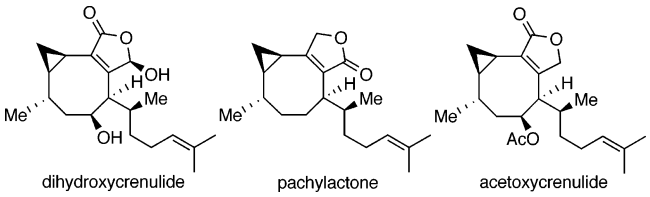
Received August 1, 2003

Abstract: A strategy to rapidly assemble enantiomerically pure bicyclo[6.1.0]nonane-9-carboxylic acids via Me_2AlOTf-promoted intramolecular Friedel−Crafts alkylation of tethered π-nucleophiles with the γ-lactone moiety of 3-oxabicyclo-[3.1.0]hexan-2-ones is described. The approach begins with the enantioselective synthesis of 3-oxabicyclo[3.1.0]hexan-2-ones bearing a tethered π-nucleophile at the 6-position by intramolecular Rh(II)-catalyzed cyclopropanation of allylic diazoacetates, prepared from the corresponding (*Z*)-allylic alcohols. Me_2AlOTf-induced intramolecular Friedel−Crafts cyclization provides medium-sized carbocycles and heterocycles in high yields without requiring high-dilution or slow substrate addition techniques. The scope and limitations of this synthetic methodology are presented.

Dihydroxycrenulide, pachylactone, and acetoxycrenulide are members of the crenulide family, a small but important group of natural diterpenoids that contain an unusual bicyclo[6.1.0]nonane skeleton fused to a butenolide (Scheme 1).[1] Acetoxycrenulide, isolated from the sea hare *Aplysia vaccaria*, has been postulated to act as a chemical defense against herbivorous reef-dwelling fish as a result of its high toxicity at very low concentrations (10 μg/mL).[2] The most synthetically challenging feature of the crenulide diterpenoids is the highly substituted eight-membered carbocyclic central core that contains up to five stereocenters. Synthetic efforts reported by Paquette and co-workers have resulted in the enantioselective total synthesis of acetoxycrenulide in 1995.[3] The eight-membered carbocyclic framework was accessed via a Claisen ring-expansion rearrangement. Formation of the medium-sized ring proceeded in modest yield mainly due to the instability of the Claisen precursor, a vinyl ether, and the forceful conditions required to promote the [3.3] sigmatropic rearrangement. A highly stereoselective Simmons−Smith cyclopropanation completed the synthesis of the bicyclo[6.1.0]nonane skeleton.

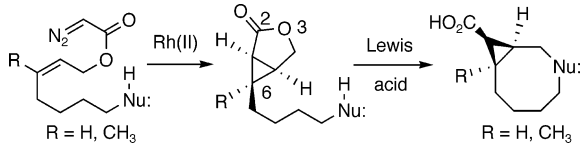
SCHEME 1. Crenulide Diterpenoids



In view of the observations made by Paquette and the difficulties generally associated with eight-membered carbocycle and heterocycle formation, the development of synthetic strategies for their rapid and efficient construction is of interest.[4]

We report here a new method for the direct conversion of 3-oxa-bicyclo[3.1.0]hexan-2-ones into bicyclo[6.1.0]-nonane-9-carboxylic acid derivatives. The strategy, illustrated in Scheme 2, begins with readily available (*Z*)-allylic diazoacetates. Intramolecular Rh(II)-catalyzed alkene cyclopropanation provides the 3-oxabicyclo[3.1.0]-hexan-2-one cyclization precursors bearing a tethered π-nucleophile at the 6-position, in a highly enantioselective fashion. The γ-lactone moiety of the bicyclic precursor then participates with π-nucleophiles in a Lewis acid-promoted intramolecular Friedel−Crafts alkylation,[5] leading to enantiomerically pure eight-membered carbo- and heterocyclic carboxylic acids.

SCHEME 2. General Strategy



The viability and scope of the proposed strategy to efficiently assemble bicyclo[6.1.0]nonanes were established by the synthesis of 3-oxabicyclo[3.1.0]hexan-2-one cyclization precursors with varied nucleophilic moieties and substituents at the 6-position. π-Nucleophiles were rationally selected for their tolerance to strong Lewis acidic conditions required to promote the Friedel−Crafts alkylation reaction. The synthesis of the substrates bearing a methyl group at the 6-position is illustrated in Scheme 3.

Neryl acetate was first transformed to alcohol **1** in three steps (Scheme 3).[6] The monoacetylated diol **1** was brominated and the acetate subsequently removed and then replaced by a TIPS protecting group yielding

(1) (a) König, G. M.; Wright, A. D.; Sticher, O. *Tetrahedron* **1991**, *47*, 1399−1410. (b) Tringali, C.; Oriente, G.; Piattelli, M.; Geraci, C.; Nicolosi, G.; Breitmaier, E. *Can. J. Chem.* **1988**, *66*, 2799−2802. (c) Kusumi, T.; Muanza-Nkongolo, D.; Gota, M.; Ishitsuka, M.; Iwashita, T.; Kakisawa, H. *J. Org. Chem.* **1986**, *51*, 384−387. (d) Ishitsuka, M.; Kusumi, T.; Kakisawa, H.; Kawakami, Y.; Nagai, Y.; Sato, T. *Tetrahedron Lett.* **1983**, *24*, 5117−5120.

(2) (a) Sun, H. H.; McEnroe, F. J.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 1903−1906. (b) Midland, S. L.; Wing, R. M.; Sims, J. J. *J. Org. Chem.* **1983**, *48*, 1906−1909.

(3) (a) Wang, T.-Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 1309−1318. (b) Paquette, L. A.; Wang, T.-Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455−1456. (c) Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435−1447.

(4) For an excellent review, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821.

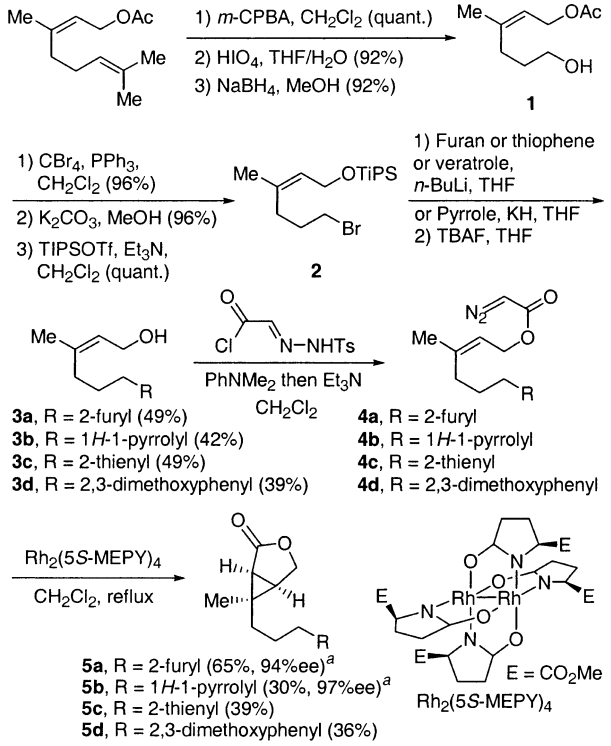
(5) For reviews on the Friedel−Crafts alkylation reaction, see: (a) Olah, G. A.; Krishnamurti, A. R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339. (b) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, 1984.

(6) (a) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269−5278. (b) For a similar transformation of geraniol acetate, see: Tago, K.; Arai, M.; Kogen, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2073−2078.

10.1021/jo0351419 CCC: $25.00
Published on Web 10/29/2003

bromide **2**. Alkylation of 2-lithiofuran with bromide **2** followed by removal of the silyl group provided the allylic alcohol **3a**. Diazoacetate **4a** was prepared from glyoxylic acid chloride *p*-toluenesulfonylhydrazone[7] in accordance with a modification of the Corey and Myers procedure.[8] An optimal yield was obtained when freshly prepared acid chloride was added to a solution of the allylic alcohol and freshly distilled *N*,*N*-dimethylaniline. Most important was the removal of the excess glyoxylic acid chloride *p*-toluenesulfonylhydrazone by filtration over a pad of silica gel following the extraction and prior to the in vacuo removal of the solvent. When the filtration was omitted, the excess acid chloride reacted with the π-nucleophile upon concentration and resulted in yield erosion.

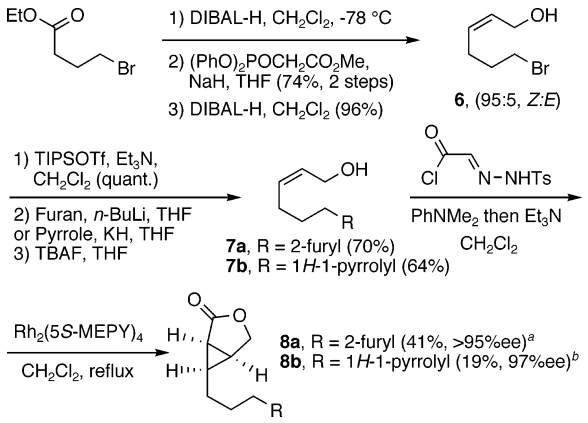
SCHEME 3. Synthesis of Cyclization Precursors 5a−d



[a] Determined by HPLC using chiral OD columns.

A second problem encountered in the preparation of the allylic diazoacetate was the well-known competitive formation of *p*-toluenesulfinate ester that arises from Et_3N-induced decomposition of glyoxylic acid chloride *p*-toluenesulfonylhydrazone. The *p*-toluenesulfinate ester byproduct could be tediously separated from the allylic diazoacetate by chromatography, but it was found that its presence had a negligible effect on the efficiency of the cyclopropanation reaction and the overall yield for the two steps was unaffected. An operationally simple two-step protocol for the formation of the 3-oxabicyclo-[3.1.0]hexan-2-ones starting from allylic alcohols was therefore adopted in which the crude allylic diazoacetates were directly cyclopropanated. The contaminated diazoacetate **4a** was cyclopropanated using Rh_2(5*S*-MEPY)$_4$ catalyst (0.5 mol %) providing bicycle **5a** in 65% yield for two steps starting from the allylic alcohol **3a**.[9,10] An enantiomeric excess of 94% was obtained for **5a**, and consequently, the absolute stereochemistry of the cyclopropane was assumed by comparison to Doyle's results obtained on similar models.[9a] The preparation of substrates **5b**−**d** followed the same sequence of steps, and the yields and enantiomeric excesses for the acylation/cyclopropanation are reported in Scheme 3. The enantioselectivity of the cyclopropanation was not affected by the pyrrole moiety and **5b** obtained in 97%ee (Scheme 3). The ee's for compounds **5c** and **5d** were not determined.

SCHEME 4. Preparation of Cyclization Precursors 8a,b



[a] Determined by ^{1}H NMR using Eu(hfc)$_3$. [b]Determined by HPLC using chiral OD columns.

Bicyclic substrates bearing a hydrogen atom at the 6-position in place of a methyl group were prepared from ethyl 4-bromobutyrate (Scheme 4). Ester reduction to the aldehyde[11] using DIBAL-H at −78 °C and subsequent Horner−Emmons reaction under Ando's conditions led to an α,β-unsaturated ester.[12] Reduction of the resulting ester provided allylic alcohol **6** as an inseparable mixture of isomers (95:5 *Z*/*E*) that was carried over the entire sequence of steps. Protection of alcohol **6** followed by alkylation with 2-lithiofuran and deprotection yielded the allylic alcohol **7a** in good yield. Preparation of the diazoacetate was carried out as before, and the purification problems described above were encountered. Cyclo-

(7) Blankley, C. J.; Sauter, F. J.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 258−263.

(8) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559−3562.

(9) (a) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763−5775. For reviews on asymmetric cyclopropanation, see: (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050. (c) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919−7946. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (e) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.

(10) For the preparation of the MEPY catalyst, see: (a) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Kazala, A. P.; Westrum, L. J. *Org. Synth.* **1996**, *73*, 13−24. (b) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968−9978.

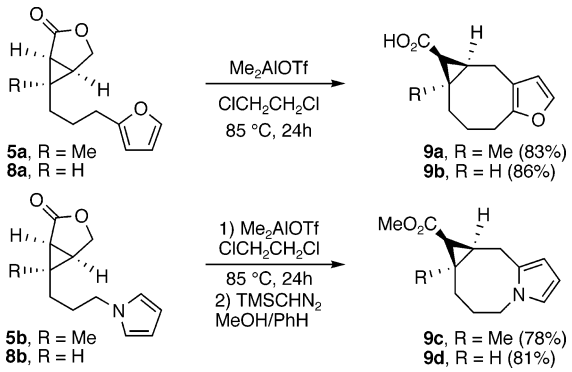
(11) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127−8134.

(12) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939.

propanation of the contaminated diazoacetate gave cyclopropane **8a** in good yield and enantioselectivity as shown in Scheme 4. Cyclopropane **8b** was prepared from the allylic alcohol **7b** in 97% ee, but with a modest yield overall (Scheme 4).

Studies of the intramolecular Friedel−Crafts alkylation were initiated with substrate **5a**. A wide variety of reaction conditions and Lewis acids ($EtAlCl_2$, Et_2AlCl, $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $Mg(OTf)_2$, TMSOTf, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$) were investigated to induce the cyclization. Et_2AlCl promoted the Friedel−Crafts alkylation yielding the desired eight-membered carbocycle, but Me_2AlOTf in $ClCH_2CH_2Cl$ was a superior Lewis acid with respect to yield and reproducibility.[13] The operationally simple and optimized protocol did not require high dilution or slow substrate addition. A Me_2AlOTf solution in $ClCH_2CH_2Cl$ was freshly prepared in a resealable Schlenk tube from Me_3Al and TfOH, to which the substrate was added. Four equivalents of Me_2AlOTf was required for the reaction to proceed to completion. The resulting cloudy solution was heated at 85 °C for 24 h, and the final product was purified by HPLC on a normal-phase semipreparative column. As illustrated in Scheme 5, cyclopropane **5a** gave the desired eight-membered carbocycle **9a** in an excellent 83% yield under these conditions.[14] The structure of **9a** was confirmed by COSY and NOESY NMR experiments on the corresponding primary alcohol, prepared by $LiAlH_4$ reduction.[15]

SCHEME 5. Scope of the Bicyclo[6.1.0]nonane Synthesis



The optimized reaction conditions were applied to other substrates. It was essential to determine if the intramolecular Friedel−Crafts alkylation would proceed for substrates having a hydrogen substituent at the 6-position instead of a methyl group since the crenulane natural products possess hydrogens at the bicyclo[6.1.0]-nonane ring junction. Comparison of cyclopropanes **5a** and **8a** reveals that the nature of the substituent on the cyclopropane (Me vs H) does not affect the cyclization process, and good yields are obtained in both cases (Scheme 5). Eight-membered heterocycles were prepared from π-nucleophilic N-substituted pyrrole precursors **5b** and **8b**. Lewis acid-promoted intramolecular Friedel−Crafts alkylation yielded the desired eight-membered-ring carboxylic acids that proved difficult to purify. In addition, some signals in the ^1H and ^{13}C NMR spectra were unresolved due to slow conformer interconversion. The purification of the bicyclo[6.1.0]nonanes was simplified by treating the crude carboxylic acids with $TMSCHN_2$ to provide the corresponding methyl esters **9c** and **9d** in 78% and 81% yield, respectively, from the cyclopropane substrates (Scheme 5).[16] The ^1H and ^{13}C NMR spectra of carboxylic ester **9c** were well-resolved at rt, but **9d** still required high-temperature NMR experiments.

The π-nucleophilicity of the tethered heterocycle is crucial for the success of the intramolecular Friedel−Crafts alkylation. Substrates **5c** and **5d**, bearing the weak 2-thienyl and 2,3-dimethoxybenzene π-nucleophiles, did not undergo cyclization to form the eight-membered carbocycles.[17] Under the standard reaction conditions, the starting material was recovered for these two substrates. When the reaction was run at higher temperatures (85−130 °C) and prolonged reaction time (12−72 h), complex mixtures of dienes identified as cyclopropane-opening products were exclusively isolated.

Two plausible mechanisms may rationalize the reactivity of 3-oxabicyclo[3.1.0]hexan-2-one in the Me_2AlOTf-promoted Friedel−Crafts alkylation.[18] Childs has reported that cyclopropylcarbinyl cations have a minimum energy conformation, which is bisected or close to bisected as a result of the involvement of the cyclopropane in charge delocalization.[19] This observation suggests that complexation of the Lewis acid with the carbonyl group of the lactone moiety promotes the formation of a loosely associated ion pair that is stabilized by the adjacent cyclopropane. The π-nucleophile then undergoes cyclization with the primary carbocation to provide the corresponding eight-membered ring.[20] Concurrently, the reaction may proceed via a concerted displacement[21] in which the cyclopropane plays a significant role in the stabilization of the transition state, decreasing the energy of activation and thus favoring the unprecedented σ-C−O bond cleavage of 3-oxabicyclo[3.1.0]hexan-2-ones to yield aluminum cyclopropanecarboxylate products.[22] The S_N2 pathway, illustrated in Scheme 6, shows that the methylene bearing a partial positive charge (δ^+) is in a bisected orientation relative to the cyclopropane ring. In addition, the template effect provided by the conformationally rigid bicyclic substrate facilitates the intramolecular Friedel−

(13) Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2193−2201.

(14) Stork reported the intramolecular opening of acylcyclopropanes via homologous Michael addition of π-nucleophiles. That opening mode was not observed in our systems, see: (a) Stork, G.; Gregson, M. *J. Am. Chem. Soc.* **1969**, *91*, 2373−2374. (b) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371−2373.

(15) See the Supporting Information for details.

(16) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478.

(17) For an excellent review on π-nucleophilicity, see: Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

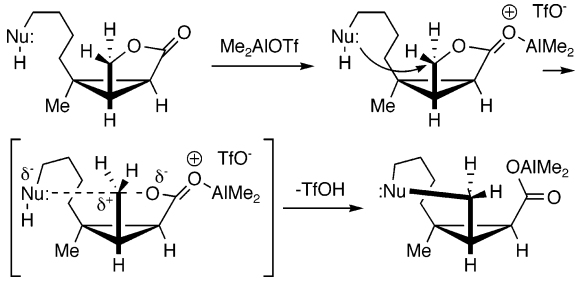
(18) Brauman, J. I.; Pandell, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 5421−5424.

(19) (a) Childs, R. F.; Kostyk, M. D.; Lock, C. J. L.; Mahendran, M. *J. Am. Chem. Soc.* **1990**, *112*, 8912−8920. (b) Childs, R. F.; Faggiani, R.; Lock, C. J. L.; Mahendran, M.; Zweep, S. D. *J. Am. Chem. Soc.* **1986**, *108*, 1692−1693.

(20) Numerous examples of Lewis acid-promoted intermolecular lactone-opening by π-nucleophiles via σ-C−O bond cleavage have been reported in the literature. In most cases, the carbinol carbon is substituted by alkyl groups or benzylic, favoring the formation of a secondary, tertiary, or benzylic carbocation and the S_N1 pathway. See ref 5.

(21) Ghatak, U. R.; Chatterjee, N. R.; Sanyal, B. *J. Org. Chem.* **1979**, *44*, 1992−1999.

SCHEME 6. Friedel–Crafts Alkylation Mechanism



Crafts alkylation. The requirement of excess Lewis acid is attributed to the likely formation of a complex aggregate of the substrate and Lewis acid in the activation stage that is common for aluminum Lewis acids.[23] When weak π-nucleophiles such as thiophene and veratrol are involved, activation of the lactone moiety by the Lewis acid induces the σ-C–O bond cleavage and formation of the associated ion pair but rearrangement of the cyclopropane is probably faster than Friedel–Crafts alkylation.

In summary, an efficient method for the synthesis of enantiomerically pure bicyclo[6.1.0]nonane-9-carboxylic acid derivatives from 3-oxabicyclo[3.1.0]hexan-2-ones has been described. Efforts are currently directed at the application of this methodology to the synthesis of crenulide natural products. These results will be reported in due course.

Experimental Section

General Procedure for the Intramolecular Friedel–Crafts Alkylation. (6a*R*,7*R*,7a*R*)-6a-Methyl-5,6,6a,7,7a,8-hexahydro-4*H*-cyclopropa[4,5]cycloocta[*b*]furan-7-carboxylic Acid (9a). To a solution of $AlMe_3$ (1.4 mL, 2.0 M solution in hexanes, 2.7 mmol) in $ClCH_2CH_2Cl$ (2 mL) at 0 °C in a resealable Schlenk tube was added TfOH (241 μL, 2.72 mmol) dropwise. After the addition was complete, the cloudy white solution was stirred for 30 min at 0 °C. A solution of 3-oxabicyclo-[3.1.0]hexan-2-one **5a** (150 mg, 0.681 mmol) in $ClCH_2CH_2Cl$ (2 mL) was cannulated into the Schlenk tube. After warming to rt, the sealed tube was placed into an 85 °C oil bath and stirred for 24 h. The reaction was quenched with cold 5% HCl (50 mL) and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by HPLC on a normal-phase semipreparative column (100% hexanes for 15 min followed by 98:2 hexanes/*i*-PrOH, flow rate 7.0 mL/min, retention time = 25.4 min) provided **9a** (125 mg, 83%) as a clear colorless oil: $[\alpha]^{22}_D$ +45.6 (*c* 0.45, $CHCl_3$); IR (neat, cm^{-1}) 2930, 2865, 1689, 1506, 1441, 1384, 1348, 1311, 1287, 1226; ^1H NMR (300 MHz, $CDCl_3$) δ 10.7 (1H, brs), 7.12 (1H, d, J = 1.7 Hz), 6.18 (1H, d, J = 1.7 Hz), 3.04 (1H, dddd, J = 15.4, 10.1, 5.0, 4.5 Hz), 2.86 (1H, ddd, J = 15.5, 8.0, 3.1 Hz), 2.64 (1H, ddd, J = 15.1, 8.5, 3.4 Hz), 2.55 (1H, dd, J = 15.8, 3.9 Hz), 2.24 (1H, m), 1.77 (3H, m), 1.54 (2H, q, J = 3.9 Hz), 1.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 152.4, 138.7, 118.7, 112.5, 36.4, 30.5, 29.9, 27.6, 27.2, 26.2, 24.9, 20.0; HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1094.

(6a*R*,7*R*,7a*S*)-5,6,6a,7,7a,8-Hexahydro-4*H*-cyclopropa-[4,5]cycloocta[*b*]furan-7-carboxylic Acid (9b). The reaction was carried out as in the general procedure for the intramolecular Friedel–Crafts alkylation using cyclopropane **8a** (150 mg, 0.727 mmol), $AlMe_3$ (1.5 mL, 2.0 M solution in hexanes, 2.9 mmol), TfOH (257 μL, 2.91 mmol), and $ClCH_2CH_2Cl$ (2 mL). Purification by HPLC (retention time = 23.0 min) provided **9b** (129 mg, 86%) as a clear colorless oil: $[\alpha]^{22}_D$ +73.1 (*c* 0.25, $CHCl_3$); IR (neat, cm^{-1}) 2928, 2860, 2687, 2543, 1689, 1511, 1444, 1348, 1300, 1213; ^1H NMR (300 MHz, $CDCl_3$) δ 11.1 (1H, brs), 7.15 (1H, d, J = 1.8 Hz), 6.17 (1H, d, J = 1.6 Hz), 3.01 (1H, dd, J = 16.4, 10.7 Hz), 2.94 (1H, m), 2.68 (1H, m), 2.64 (1H, dd, J = 16.1, 4.9 Hz), 1.90 (3H, m), 1.80 (1H, m), 1.73 (1H, m), 1.62 (1H, m), 1.39 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 151.5, 138.8, 118.1, 112.8, 27.5, 26.5, 25.7, 25.4, 22.1, 21.4, 19.2; HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0942.

Methyl (1*R*,1a*R*,9a*R*)-1a-Methyl-1a,2,3,4,9,9a-hexahydro-1*H*-cyclopropa[*f*]pyrrolo[1,2-*a*]azocine-1-carboxylate (9c). The Friedel–Crafts reaction was carried out as in the general procedure for the intramolecular Friedel–Crafts alkylation using cyclopropane **5b** (20 mg, 0.091 mmol), $AlMe_3$ (182 μL, 2.0 M in hexanes, 365 mmol), TfOH (32.3 μL, 365 mmol), and $ClCH_2CH_2$-Cl (2 mL). The crude oil was filtered through a pad of silica gel, eluted with Et_2O, and concentrated. The oil was then dissolved in MeOH/PhH (0.5 mL/1.5 mL), treated with $TMSCHN_2$ (60 μL, 2.0 M solution in hexanes, 0.119 mmol), and stirred for 30 min at rt. The solvent was removed in vacuo and the residue purified by HPLC (retention time = 24.6 min) to provide **9c** (16.5 mg, 78%) as a clear colorless oil: $[\alpha]^{22}_D$ +68.7 (*c* 0.12, $CHCl_3$); IR (neat, cm^{-1}) 3100, 2952, 2917, 2856, 1718, 1485, 1466, 1439, 1369, 1301, 1274, 1234; ^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (1H, t, J = 2.0 Hz), 5.99 (1H, t, J = 3.0 Hz), 5.91 (1H, brs), 4.04 (1H, dd, J = 14.9, 6.3 Hz), 3.84 (1H, dd, J = 14.5, 10.8 Hz), 3.66 (3H, s), 3.13 (1H, dd, J = 15.0, 11.9 Hz), 2.81 (1H, m), 2.47 (1H, m), 1.86 (2H, m), 1.71 (1H, dd, J = 14.8, 7.5 Hz), 1.49 (1H, d, J = 8.2 Hz), 1.34 (1H, ddd, J = 12.1, 8.6, 3.7 Hz), 1.05 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 133.2, 121.7, 106.5, 106.1, 51.5, 51.3, 50.9, 36.6, 29.7, 29.1, 28.0, 26.4, 21.9; HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1416, found 233.1412.

Methyl (1*S*,1a*R*,9a*S*)-1a,2,3,4,9,9a-Hexahydro-1*H*-cyclopropa[*f*]pyrrolo[1,2-*a*]azocine-1-carboxylate (9d). The Friedel–Crafts reaction was carried out as in the general procedure for the intramolecular Friedel–Crafts alkylation using cyclopropane **8b** (20 mg, 0.097 mmol), $AlMe_3$ (195 μL, 2.0 M solution in hexanes, 0.390 mmol), TfOH (34.5 μL, 0.390 mmol), and $ClCH_2CH_2Cl$ (2 mL). The crude oil was filtered through a pad of silica gel, eluted with Et_2O, and concentrated. The oil was then dissolved in MeOH/PhH (0.5 mL/1.5 mL), treated with $TMSCHN_2$ (63 μL, 2.0 M solution in hexanes, 0.127 mmol), and stirred for 30 min at rt. The solvent was removed in vacuo and the residue purified by HPLC (retention time = 24.8 min) to provide **9d** (17.3 mg, 81%) as a clear colorless oil: $[\alpha]^{22}_D$ +26.6 (*c* 0.33, $CHCl_3$); IR (neat, cm^{-1}) 2920, 2848, 1721, 1637, 1487, 1447, 1374, 1447, 1374, 1349, 1320, 1302, 1283, 1269, 1232; ^1H NMR (500 MHz, 363K, DMSO-d_6) δ 6.55 (1H, t, J = 2.1 Hz), 5.88 (1H, t, J = 3.0 Hz), 5.80 (1H, m), 4.07 (1H, ddd, J = 14.4, 9.4, 3.4 Hz), 3.81 (1H, ddd, J = 14.5, 5.9, 4.1 Hz), 3.59 (3H, s), 3.14 (1H, dd, J = 15.3, 4.8 Hz), 2.68 (1H, dd, J = 15.1, 7.0 Hz), 2.06 (1H, m), 1.84 (1H, m), 1.55 (2H, m), 1.35 (1H, dddd, J = 15.9, 5.0, 4.9, 4.8 Hz), 1.23 (1H, t, J = 4.7 Hz), 0.60 (1H, m); ^{13}C NMR (125 MHz, 363 K, DMSO-d_6) δ 172.8, 130.1, 120.8, 106.2, 106.1, 50.6, 45.9, 29.5, 27.8, 25.7, 25.2, 24.8, 23.9; HRMS (EI) *m*/*z* calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1259, found 219.1255.

Acknowledgment. The Natural Science and Engineering Research Council of Canada (NSERC) and the University of Waterloo are thanked for financial support. R.L.B. thanks NSERC for a PGS A fellowship.

Supporting Information Available: Detailed experimental procedures and full characterization data for compounds **1**, **2**, **3a**–**d**, **5a**–**d**, **6**, **7a**,**b**, **8a**,**b** and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0351419

(22) No experimental evidence is available to determine if the triflate dissociates in the complexation process of Me_2AlOTf with the lactone. In addition, no attempts were made to identify likely side products such as methane or TfOH generated in the course of the Friedel–Crafts alkylation.

(23) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391–4399.