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Diastereoselective Synthesis of Allosecurinine and Viroallosecurinine from Menisdaurilide

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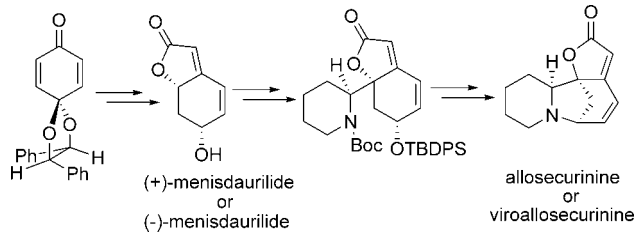
Received July 4, 2008



A new and versatile synthetic route to *Securinega* alkaloids is reported. The first synthesis of allosecurinine has been accomplished in seven steps and 40% yield, starting from (+)-menisdaurilide, using a vinylogous Mannich reaction as the key transformation. Similarly, viroallosecurinine has been synthesized from (−)-menisdaurilide.

The *Securinega* alkaloids include a large number of polycyclic compounds elaborated mainly by plants of the genus *Securinega* and *Phyllanthus* belonging to the Euphorbiaceae family.[1] Some of these alkaloids exhibit several pharmacological activities, including diuretic, hepatic protection, antimicrobial, antibacterial, and $GABA_A$ receptor antagonism, among others.[2] The most representative examples of these alkaloids are securinine **1**, first isolated in 1956,[3] its epimer at C-2, allosecurinine **2**, their corresponding enantiomers, virosecurinine and viroallosecurinine, respectively, and (−)-norsecurinine **3** (Figure 1). Most *Securinega* alkaloids present a tetracyclic structure, enclosing a benzofuranone subunit (rings C and D) and either a piperidine or pyrrolidine ring (ring A), with the size of this last ring characterizing the securinine- and norsecurinine-type subgroups, respectively.

The biosynthesis of *Securinega* alkaloids received particular attention in the 1970s (Scheme 1). On the basis of experiments performed with labeled precursors, it was established that the piperidine ring A of securinine is derived from a C_5N subunit (Δ^1-piperidine **7**), formed from lysine in a nonsymmetrical

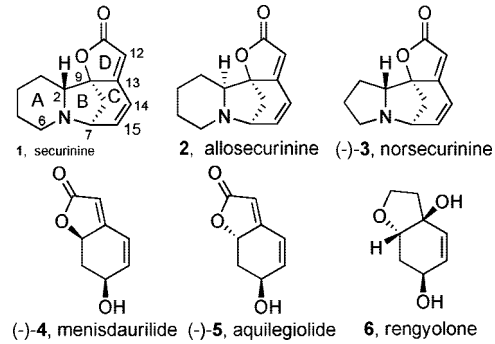


FIGURE 1. Representative examples of *Securinega* alkaloids and other natural products.

fashion,[4] whereas the rings C and D (ArC_2 subunit) come from tyrosine,[4b,5] which is in turn biosynthesized from shikimic acid.

In 1978 Parry proposed a biosynthesis of *Securinega* alkaloids consistent with the former experiments (Scheme 1, path a).[5] According to his proposal, tyrosine would be initially transformed into bicyclic intermediate **8**, where rings A and C are already present. The route would continue with an intramolecular 1,4-addition to close ring D, furnishing the tricyclic precursor **9**, and the subsequent reduction of the carbonyl group would

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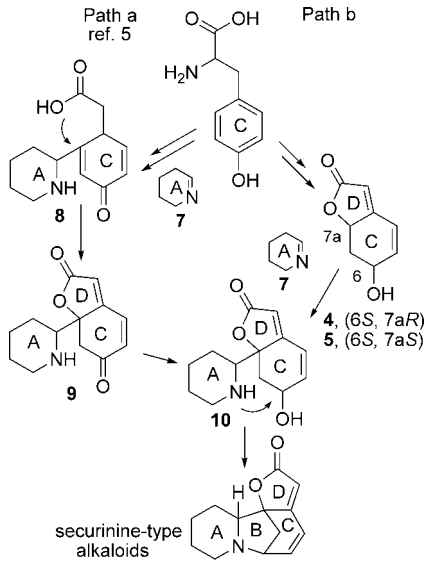
10.1021/jo801470u CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/10/2008

SCHEME 1. Putative Biosynthesis of Securinine: Path a, Parry's Proposal; Path b, Alternative Route



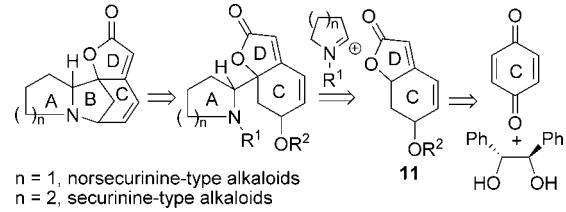
generate the intermediate **10**. Finally, an intramolecular nucleophilic substitution would afford the tetracyclic structure.

In 1984, the isomeric bicyclic lactones menisdaurilide (−)-**4** and its epimer, aquilegiolide (−)-**5** (Figure 1), were isolated for the first time from *Aquilegia atrata*.[6] Both epimers have been isolated from other plants of the genus *Phyllanthus*[7−9] and *Securinega*.[10] This last work reports for the first time the simultaneous extraction of the bicyclic lactones **4** and **5** and several *Securinega* alkaloids, among them securinine, from the same plant. Studies about the biosynthesis of menisdaurilide or aquilegiolide have not been reported, although a plausible biosynthetic route for the related compound rengyolone **6** from shikimic acid has been proposed.[11]

The structural similarity of **4** and **5**, matching rings C and D of the aforementioned *Securinega* alkaloids, the reported isolation of all these natural products from plants of the same genus *Phyllanthus* and *Securinega*, along with the recently discovered common natural source, led us to consider the possibility that the benzofuranones **4** and/or **5** could be intermediates in the biosynthesis of the alkaloids. According to this alternative biosynthetic route (Scheme 1, path b), the formation of the benzofuranone skeleton (rings C and D of the alkaloids) would precede the coupling with the C_5N subunit (ring A of the alkaloids) to afford the amino alcohol **10**. This route would be equally consistent with the labeling experiments described.[4,5]

In the past decade, we have been working in the synthesis of *Securinega* alkaloids and have already described a diastereoselective synthesis of securinine and (−)-allonorsecurinine based on materials from chiral pool[12] and an enantioselective preparation of (−)-norsecurinine[13] based on the use of asymmetric catalysis. Our group has also developed a highly efficient

SCHEME 2. Retrosynthetic Analysis



diastereoselective synthesis of both antipodes of menisdaurilide, starting from *p*-benzoquinone and using (*R*,*R*)-hydrobenzoin as a chiral auxiliary.[14]

With our biosynthetic considerations about *Securinega* alkaloids in mind, we envisaged a novel stereoselective synthesis of these alkaloids starting from menisdaurilide (Scheme 2). The key step of this new approach would be a vinylogous Mannich reaction[15] to connect the benzofuranone fragment **11** (rings C and D), closely related to menisdaurilide, with the C_5N or C_4N subunit (ring A), generating two of the three stereogenic centers present in the targets. Both antipodes of menisdaurilide **4** would be synthesized according to our reported procedure.[14]

Among the 14 publications describing total syntheses of *Securinega* alkaloids,[2b,12,13,16] only that reported by Liras et al.[16g] made use of a vinylogous Mannich reaction involving a C_5N electrophilic synthon, but the nucleophilic partner was not related with any possible biogenetic precursor.

Herein we present a new diastereoselective synthesis of the two *Securinega* alkaloids allosecurinine **2**, and its enantiomer, viroallosecurinine, through a straightforward sequence based upon the retrosynthetic analysis outlined in Scheme 2.

Results and Discussion

We initiated our studies starting from the benzofuranone ketal **12** (Scheme 3), accessible in a 45% yield from *p*-benzoquinone,[14,17] and used as an advanced intermediate in our previously mentioned synthesis of (+)-menisdaurilide (+)-**4**.[14] The ketal would serve both as a chiral directing group for the vinylogous Mannich reaction and as a carbonyl protecting group. The compound **13**[18] was selected as the C_5N synthon.

Thus, the (7a)-epimeric mixture of **12** was treated with triethylamine and triisopropylsilyl triflate (TIPSOTf) to furnish the corresponding silyloxyfuran **14**. The vinylogous Mannich reaction between **14** and the piperidinium ion generated in situ from **13** was accomplished using 1 equiv of TIPSOTf as Lewis

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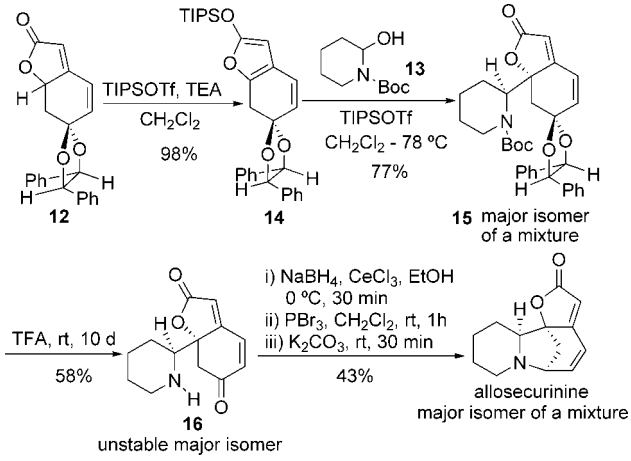
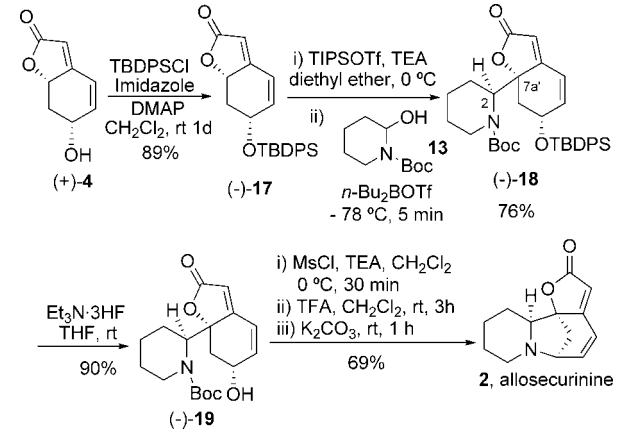
SCHEME 3. Diastereoselective Synthesis of Allosecurinine, First Approach



SCHEME 4. Diastereoselective Synthesis of Allosecurinine



acid in CH_2Cl_2 at −78 °C, affording in 77% yield an inseparable mixture of only two (among the four possible) diastereomeric condensation products **15** in a ca. 5:1 ratio (Scheme 3), according to its ^{1}H NMR spectrum, which shows two sets of signals due to the presence of the two diastereomers. Moreover, for the major diastereomer, two signals corresponding to two rotamers, in a proportion of ca. 4:1, are observed for some protons. This assignment was corroborated with variable temperature ^{1}H NMR experiments and NOESY experiments, where exchange signals between absorptions of the same proton but corresponding to different rotamers were observed. The absolute configuration of the major isomer was later established as (2*S*,7a′*S*) by chemical correlation (vide infra).

The stereochemical outcome of the reaction is consistent with the preferential formation of a *threo* adduct, through a "Diels-Alder"-like transition state, according to Martin studies,[15] and the facial selectivity of the furan induced by the bulky ketal moiety (Figure 2a).

To complete the remaining steps leading to allosecurinine outlined in Scheme 3, the 5:1 mixture of isomers **15** was used, although only the main isomer is depicted. Thus, the selective hydrolysis of the ketal group of **15** was tried under different experimental conditions but could not be achieved, since concomitant deprotection of Boc group was always observed. As the best result, by treating **15** with trifluoroacetic acid (TFA), the unstable aminoketone **16** could be isolated in 58% yield.

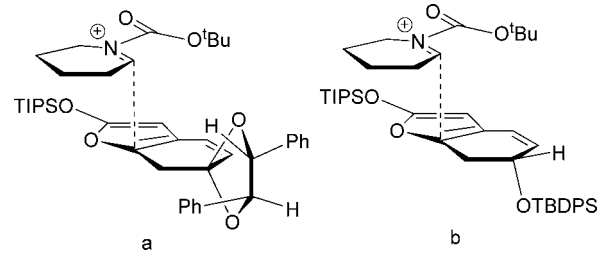


FIGURE 2. Preferred transition states for the vinylogous Mannich reactions.

Ketone **16** was reduced with $NaBH_4$ in presence of $CeCl_3$[19] to furnish, essentially, a 1:1 mixture of the corresponding diastereomeric alcohols in 58% yield, along with several degradation products with phenolic structure. The ca. 1:1 mixture of alcohols was sequentially treated with PBr_3 to afford the corresponding allylic bromides and aqueous K_2CO_3 solution to yield, in 75% yield for the two steps, a sample of the final alkaloid, pure enough to be identified as allosecurinine according to its ^{1}H NMR data and negative value of its specific rotation. Following this experimental methodology, both intermediate bromide derivatives proved to be reactive enough in the final cyclization step to give the target alkaloid, despite the fact that every diastereomer is expected to react through a different mechanism and with distinct reaction rates.[16j]

The lack of orthogonality of the protecting groups, along with the instability of the intermediate ketone **16**, were two major problems encountered across the above synthetic route. The tactical modification to overcome these problems was starting the synthesis from menisdaurilide **4** itself (Scheme 4).

Thus, the hydroxyl group of (+)-**4** was protected as the *tert*-butyldiphenylsilyl ether affording compound (−)-**17** in 89% yield (Scheme 4). This compound was treated with TIPSOTf and TEA at 0 °C to furnish the corresponding silyloxyfuran, which without further purification was used to react with the piperidinium ion generated in situ from **13**, under the vinylogous Mannich reaction conditions. Thus, the condensation reaction was accomplished using 1 equiv of n-Bu_2BOTf as Lewis acid in diethyl ether at −78 °C, giving a mixture of only two (among the four possible) diastereomeric products in a ca. 4:1 ratio and almost quantitative yield. Remarkably, these two isomers proved to be easily separable by standard flash chromatography, allowing the isolation of the major isomer (−)-**18** in 76% yield (Scheme 4). The ^{1}H NMR spectrum of (−)-**18** shows two sets of signals, due to the presence of two rotamers, in a proportion of 6:1. This assignment was corroborated with variable temperature ^{1}H NMR and NOESY experiments, where exchange signals between absorptions of the same proton but corresponding to different rotamers were observed. This behavior, to a lesser extent, can be guessed too in the ^{13}C NMR spectrum. The absolute configuration of (−)-**18** was unambiguously established as (2*S*,7a′*S*) by chemical correlation (vide infra) with the natural alkaloid allosecurinine **2**. The stereochemical outcome of the reaction is also consistent with the preferential formation of a *threo* adduct, according to Martin studies,[15] and the facial selectivity of the furan, now induced by the silyloxy-ether substituent (Figure 2b).

Removal of the silyl protecting group in (−)-**18** using $Et_3N{\cdot}3HF$ reagent led efficiently (90% yield) to the alcohol (−)-**19**. Again, the ^{1}H NMR spectrum of this compound shows two

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sets of signals due to the presence of two rotamers; in this case, the proportion between rotamers is 83:17. This assignment was corroborated, as in previous cases, with variable temperature ^{1}H NMR and NOESY experiments. Sequential mesylation of alcohol (−)-**19** with MsCl and TEA, removal of the carbamate group using TFA, and then treatment of the reaction mixture with aqueous K_2CO_3 solution afforded the alkaloid allosecurinine **2** in 69% overall yield for the three last steps, without isolation of any of the involved intermediates. The optical rotation of the synthetic material {$[\alpha]_D$ −1092 (*c* 1.0, EtOH)} is in agreement with the previously reported values {lit. −1082 (EtOH),[20] −1004 (MeOH),[21] −1082 (EtOH),[22] −1140[23]}. Hence, the first synthesis of allosecurinine **2** has been completed, in a seven-step sequence and 42% overall yield, starting from (+)-menisdaurilide (+)-**4**. Considering our previous synthesis of (+)-**4**,[14] starting from *p*-benzoquinone and using (*R*,*R*)-hydrobenzoin as a chiral auxiliary, the synthesis of allosecurinine **2** has been accomplished in 14 steps and 4.4% overall yield.

The same synthetic sequence depicted in Scheme 4 was also performed starting from (−)-menisdaurilide (−)-**4**, giving access to the alkaloid viroallosecurinine in 38% overall yield from (−)-**4**, 3.8% from *p*-benzoquinone, {$[\alpha]_D$ +1068 (*c* 1.2, EtOH), [lit. +1084.6 (EtOH),[24] +1200 (EtOH),[25] +990 (EtOH),[26] +1113 (EtOH)[16j]]}.

Conclusions

In summary, a new diastereoselective synthesis of two *Securinega* alkaloids has been developed, using a vinylogous Mannich reaction as the key transformation. The first synthesis of allosecurinine has been accomplished, in seven steps and around 40% yield, starting from (+)-menisdaurilide (+)-**4**. Similarly, viroallosecurinine has been synthesized, in seven steps and 38% yield, from (−)-menisdaurilide (−)-**4**. The reported procedure is susceptible to be extended to the synthesis of norsecurinine-type alkaloids.

Experimental Section

General experimental details are provided in Supporting Information.

(6*R*,7a*S*)-6-(*tert*-Butyldiphenylsilanyloxi)-7,7a-dihydrobenzofuran-2(6*H*)-one (17). To a solution of (+)-menisdaurilide **4** (270 mg, 1.75 mmol), imidazole (369 mg, 5.42 mmol) and DMAP (21 mg, 0.17 mmol) in anhydrous dichloromethane (18 mL), *tert*-butylchlorodiphenylsilane (490 μL, 1.85 mmol) was added dropwise, and the mixture was allowed to stir overnight at room temperature. The mixture was quenched with NH_4Cl (15 mL), extracted with dichloromethane (3 × 25 mL,) and dried ($MgSO_4$). After concentration in vacuo the crude was purified by flash chromatography with *n*-hexane/AcOEt (10:1 to 1:2) affording (−)-**17** (605 mg, 1.55 mmol, 89% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75−7.60 (m, 4H, H-ar), 7.53−7.33 (m, 6H, H-ar), 6.46 (dd, *J* = 10.0, 2.4 Hz, 1H: H-4), 6.21 (d, *J* = 10.0 Hz, 1H, H-5), 5.75 (br s, 1H, H-3), 4.63 (ddd, *J* = 13.4, 4.9, 1.7 Hz, 1H, H-7a), 4.55−4.51 (m, 1H, H-6), 2.67 (ddd, *J* = 11.1, 5.2, 4.8 Hz, 1H, H-7eq), 1.79 (ddd, *J* = 13.4, 11.0, 10.3 Hz, 1H, H-7'ax), 1.09 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 163.1, 144.4, 135.9, 133.1, 130.2, 128.0, 119.5, 111.2, 78.0, 68.2, 40.2, 26.9, 19.2. IR (ATR, cm^{-1}): ν 2949, 2859, 1736 (C═O st.), 1639, 1426, 1324, 1020, 702. Anal. Calcd for $C_{24}H_{26}O_3Si$: C, 73.81; H, 6.71. Found: C, 73.66; H, 6.83. HRMS (ESI+) *m*/*z*: calcd for $C_{24}H_{26}O_3SiNa$ 413.1543 (MNa^+); found 413.1550. $[\alpha]_D$ −61.2 (*c* 2.0, $CHCl_3$). Mp 109−110 °C (*n*-pentane/ether).

(6*S*,7a*R*)-6-(*tert*-Butyldiphenylsilanyloxy)-7,7a-dihydrobenzofuran-2(6*H*)-one (17). The same experimental procedure previously described for the preparation of (−)-**17** was followed, starting with (350 mg, 2.300 mmol) of (−)-menisdaurilide, **4**, and yielding (+)-**17** (819 mg, 2.10 mmol, 91% yield) as a white solid. $[\alpha]_D$ +57.0 (*c* 1.8, $CHCl_3$). Mp 109−110 °C (*n*-pentane/ether).

(2*S*,7a*S*,4″*R*,5″*R*)-*tert*-Butyl-2-{4′,5′-diphenyl-2-oxo-7,7a-dihydrospiro-[benzofuro-6(2*H*),2′-[1,3]dioxolan-7a-yl]}piperidine-1-carboxylate (15). To a solution of an isomeric mixture of **12**[14] (301 mg, 0.87 mmol) in dry CH_2Cl_2 (15 mL) under argon atmosphere and cooled to 0 °C, triethylamine (350 μL, 2.51 mmol) was added, and the reaction mixture was stirred for 45 min at 0 °C. Then, TIPSOTf (255 μL, 0.95 mmol) was added, and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated in vacuo to afford an oil that was purified by flash chromatography with *n*-hexane/AcOEt (9:1) to yield (4′*R*,5′*R*)-4′,5′-diphenyl-2-(triisopropyl)sililoxyspiro[benzofuro-6(7*H*),2′-[1,3]dioxolan] **14** (427 mg, 0.85 mmol, 98%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40−7.28 (6H, H-ar), 7.27−7.10 (4H, H-ar), 6.45 (d, *J* = 9.7 Hz, 1H, H-4), 5.80 (d, *J* = 9.7 Hz, 1H, H-5), 5.11 (s, 1H, H-3), 4.83 (s, 2H, H-4′, H-5′), 3.46 (d, *J* = 18.3 Hz, 1H, H-7), 3.33 (d, *J* = 18.3 Hz, 1H, H-7), 1.40−1.15 (m, 3H, 3C*H*(CH_3)$_2$), 1.15−1.00 (m, 18H, 3CH(CH_3)$_2$). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 156.4, 138.3, 136.2, 136.1, 128.4, 126.8, 126.7, 123.8, 123.0, 115.6, 108.5, 85.5, 84.8, 82.1, 36.0, 17.7, 12.3. EM (ESI+) *m*/*z*: 525 (M^+ + 23, 100). To a solution of **14** (556 mg, 1.11 mmol) in dry CH_2Cl_2 (20 mL) was added another solution of *tert*-butyl-2-hydroxipiperidine-1-carboxylate **13**[18] (228 mg, 1.13 mmol) in dry CH_2Cl_2 (13 mL), and the solution was cooled to −78 °C. Then, TIPSOTf (305 μL, 1.14 mmol) was added dropwise during 5 min, and the mixture was allowed to stir 45 min at −78 °C. The mixture was quenched with $NaHCO_3$ saturated solution (30 mL) and allowed to warm to room temperature. Phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford an oil. This crude material was purified by flash chromatography with *n*-hexane/AcOEt (8:1 to 4:1) to yield a colorless oil identified as a inseparable 5:1 mixture of **15** and another related isomer (572 mg, 1.08 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.25 (6H, H-ar), 7.23−7.13 (4H, H-ar), 6.78 (d, *J* = 10.0 Hz) + 6.73 (d, *J* = 10.0 Hz) (1H, H-4′), 6.31 (d, *J* = 10.0 Hz) + 6.20 (d, *J* = 10.0 Hz) (1H, H-5′), 5.91 (s) + 5.79 (s) + 5.78 (s) (1H, H-3′), 4.88 (d, *J* = 8.8 Hz) + 4.84 (d, *J* = 8.8 Hz) + 4.77 (d, *J* = 8.8 Hz) + 4.74 (d, *J* = 8.8 Hz) (2H, H-4″, H-5″), 4.67 (t, *J* = 5.9 Hz) + 4.61 (t, *J* = 6.2 Hz) + 4.55 (t, *J* = 6.2 Hz) (1H, H-2), 4.05 (dd, *J* = 13.3 Hz, *J* = 5.6 Hz) + 3.84 (dd, *J* = 13.3 Hz, *J* = 5.6 Hz) (1H, H-6), 3.10−2.87 (m, 1H, H-6), 3.11 (d, *J* = 13.8 Hz) + 3.03 (d, *J* = 12.6 Hz) (1H, H-7′), 2.29 (d, *J* = 13.8 Hz) + 2.23 (d, *J* = 13.5 Hz) + 2.22 (d, *J* = 13.5 Hz) (1H, H-7′), 2.00 (m, 1H, H-3), 1.80 (m, 2H), 1.58−1.15 (m, 3H), 1.40 (s) + 1.37 (s) + 1.35 (s) (9H, OC(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.2, 165.0, 155.6, 135.2, 133.8, 128.5, 126.5, 124.0, 112.6, 105.6, 90.0, 85.5, 85.4, 79.4, 53.6, 42.0, 40.8, 28.2, 23.7, 23.3, 18.6. IR (ATR, cm^{-1}): ν 2928, 2860, 1756 (C═O st), 1684 (C═O st), 1644, 1451, 1365, 1276, 1123, 757. EM (ESI+) *m*/*z*: 568 (M^+ + 23, 100).

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(2*S*,6′*R*,7a′*S*)-*tert*-Butyl-2-(6-(*tert*-butyldiphenylsilanyloxy)-2-oxo-7,7a-dihydro-2*H*-benzofuran-7a-yl)piperidine-1-carboxylate (18) and Its Isomer (18m). To a solution of (−)-**17** (500 mg, 1.28 mmol) in dry ethyl ether (13 mL) under argon atmosphere and cooled to 0 °C, triethylamine (360 μL, 2.57 mmol) was added, and the reaction mixture was stirred for 45 min at 0 °C. TIPSOTf (410 μL, 1.48 mmol) was added, and the reaction mixture was allowed to stir overnight at room temperature. To the reaction mixture, another solution of *tert*-butyl-2-hydroxipiperidine-1-carboxylate **13** (580 mg, 2.88 mmol) in dry ethyl ether (13 mL) was added, and the solution was cooled to −78 °C. Then, *n*-Bu_2BOTf (1000 μL, 1.0 mmol) was added dropwise during 5 min, and the mixture was allowed to stir for 5 min at −78 °C. The mixture was quenched with NH_4Cl (30 mL) and allowed to warm to room temperature. The aqueous phase was extracted with ether (2 × 30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a mixture of the two diastereomeric condensation products (−)-**18** and (+)-**18m** in a ca. 4:1 ratio. This crude material was purified by flash chromatography with *n*-hexane/AcOEt (10:1 to 5:1) to yield (−)-**18** (562 mg, 0.98 mmol, 76%) as a colorless oil and (+)-**18m** (123 mg, 0.21 mmol, 17%) as a white wax. (−)-**18**. ^{1}H NMR (400 MHz, $CDCl_3$): (ca. 86% major conformer) δ 7.79−7.56 (4H, H-ar), 7.54−7.33 (6H, H-ar), 6.52 (dd, *J* = 10.0, 2.1 Hz, 1H, H-4′), 6.25 (d, *J* = 10.1 Hz, 1H, H-5′), 5.64 (s, 1H, H-3′), 4.39 (m, 1H, H-6′), 3.82 (t, *J* = 5.9 Hz, 1H, H-2), 3.73 (dd, *J* = 13.8, 5.5 Hz, 1H, H-6), 2.90 (dt, *J* = 13.4, 5.4 Hz, 1H, H-6), 2.36 (dd, *J* = 12.4, 5.3 Hz, 1H, H-7′), 1.80 (dd, *J* = 12.2, 10.4 Hz, 1H, H-7′), 1.63−0.66 (m, 6H, 2H-3/2H-4/2H-5), 1.30 (s, 9H, OC(CH_3)$_3$), 1.06 (s, 9H, C(CH_3)$_3$); (*ca.* 14% minor conformer, observable signals) δ 6.48 (dd, *J* = 10.1, 2.1 Hz, 1H, H-4′), 6.17 (d, *J* = 10.1 Hz, 1H, H-5′), 5.74 (s, 1H, H-3′), 4.33 (m, 1H, H-6′), 3.96 (dd, *J* = 13.8, 5.5 Hz, 1H, H-6), 2.83 (dt, *J* = 13.1, 4.3 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.5, 166.1, 155.6, 139.9, 136.0, 136.0, 133.4, 133.0, 130.2, 128.1, 128.1, 121.8, 111.1, 89.7, 79.8, 67.2, 52.4, 41.6, 40.9, 28.3, 27.0, 23.7, 23.3, 19.2, 18.6. IR (ATR, cm^{-1}): ν 2932, 2857, 1751 (C═O st), 1684 (C═O st), 1405, 1365, 846, 752. HRMS (ESI+) *m*/*z*: calcd for $C_{34}H_{43}NO_5SiNa$ 596.2803 (MNa^+); found 596.2804. $[\alpha]_D$ −93.9 (*c* 2.3, $CHCl_3$). (+)-**18m**. ^{1}H NMR (400 MHz, $CDCl_3$): (ca. 64% major conformer) δ 7.86−7.57 (m, 4H, H-ar), 7.57−7.31 (m, 6H, H-ar), 6.43 (d, *J* = 9.9 Hz, 1H, H-4′), 5.65 (dd, *J* = 9.8, 4.4 Hz, 1H, H-5′), 5.59 (s, 1H, H-3′), 4.76 (t, *J* = 6.8 Hz, 1H, H-2), 4.56 (t, *J* = 4.6 Hz, 1H, H-6′), 4.07 (t, *J* = 6.7 Hz, 1H, H-6), 3.21−2.87 (m, 1H, H-6), 2.59 (d, *J* = 14.1 Hz, 1H, H-7′), 2.12−0.80 (m) (6H, 2H-3, 2H-4, 2H-5), 1.74 (dd, *J* = 14.2, 5.4 Hz, 1H, H-7′), 1.40 (s) (9H, OC(CH_3)$_3$), 1.07 (s) (9H, C(CH_3)$_3$); (ca. 36% minor conformer, observable signals) δ 6.38 (d, *J* = 9.9 Hz, 1H, H-4′), 5.71 (s, 1H, H-3′), 5.53 (dd, *J* = 9.6, 4.4 Hz, 1H, H-5′), 4.85 (t, *J* = 5.9 Hz, 1H, H-2), 4.62 (t, *J* = 4.3 Hz, 1H, H-6′), 3.87 (dt, *J* = 13.2, 3.6 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.0 + 172.2 (C-2′), 166.1 + 164.7 (C-3a'), 156.1 + 155.7 (N-CO), 136.2 + 136.1 + 135.9 + 135.8 + 133.5 + 133.3 + 133.1 + 130.3 + 130.1 + 128.1 + 128.0 (C-ar), 135.2 + 134.2 (C-5′), 122.8 + 122.6 (C-4′), 113.5 + 111.7 (C-3′), 88.9 (C-7a′), 80.2 + 79.3 (O*C*(CH_3)$_3$), 66.1 (C-6′), 54.8 (C-2), 40.7 + 40.0 (C-6), 37.9 + 37.5 (C-7′), 28.9 + 28.7 + 28.4 (OC(*C*H_3)$_3$), 27.2 (C(*C*H_3)$_3$), 24.5 + 23.7 + 23.3 + 22.3 (C-3, C-5), 19.1/18.9 (C-4), 19.3 (*C*(CH_3)$_3$). IR (ATR, cm^{-1}): ν 2931, 2858, 1751 (C═O st), 1686 (C═O st), 1401, 1364, 1148, 911, 751. HRMS (ESI+) *m*/*z*: calcd for $C_{34}H_{43}NO_5SiNa$ 596.2803 (MNa^+, 100); found 596.2815. $[\alpha]_D$ +126.7 (*c* 0.9, $CHCl_3$).

(2*R*,6′*S*,7a′*R*)-*tert*-Butyl-2-(6-(*tert*-butyldiphenylsilanyloxy)-2-oxo-7,7a-dihydro-2*H*-benzofuran-7a-yl)piperidine-1-carboxylate (18 and 18m). The same experimental procedure previously described for the preparation of (−)-**18** and (+)-**18m** was followed, starting with 500 mg (1,280 mmol) of (+)-**17** and affording (+)-**18** (529 mg, 0.922 mmol, 72%) as a colorless oil and (−)-**18m** (149 mg, 0.260 mmol, 20%) as a white wax. (+)-**18**: $[\alpha]_D$ +86.3 (*c* 2.1, $CHCl_3$). (−)-**18m**: $[\alpha]_D$ −138.6 (*c* 1.8, $CHCl_3$).

(2*S*,6′*R*,7a′*S*)-*tert*-Butyl-2-(6-hydroxy-2-oxo-7,7a-dihydro-2*H*-benzofuran-7a-yl)piperidin-1-carboxylate (19). To a solution of (−)-**18** (495 mg, 0.86 mmol) in dry THF (25 mL) under nitrogen atmosphere, $Et_3N·3HF$ (2.9 mL, 17.44 mmol) was added, and the reaction mixture was refluxed for 3.5 h. The reaction mixture was quenched with NH_4Cl (20 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford an oil that was purified by flash chromatography with *n*-hexane/AcOEt (2:1 to 1:1), yielding (−)-**19** (260 mg, 0.775 mmol, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): (83% major conformer) δ 6.57 (dd, *J* = 10.0 Hz, *J* = 2.0 Hz, 1H, H-4′), 6.20 (d, *J* = 10.0 Hz, 1H, H-5′), 5.70 (s, 1H, H-3′), 4.54 (br s, 1H, H-6′), 4.20 (t, *J* = 6.0 Hz, 1H, H-2), 3.84 (dd, *J* = 14.1, 5.3 Hz, 1H, H-6eq), 3.02 (ddd, *J* = 13.5, 12.3, 4.9 Hz, 1H, H-6ax), 2.90 (dd, *J* = 12.4, 5.5 Hz, 1H, H-7'eq), 2.28 (br, *J* = 5.8 Hz, 1H, -OH), 2.03 (m, 1H, H-3), 1.94−1.41 (m, 5H, 1H-3/2H-4/2H-5), 1.72 (dd, *J* = 12.3, 10.7 Hz, 1H, H-7'ax), 1.36 (s) (9H, C(CH_3)$_3$); (17% minor conformer, observable signals) δ 5.70 (s, 1H, H-3′), 4.14 (t, *J* = 5.4 Hz, 1H, H-2), 4.05 (dd, *J* = 13.9, 5.2 Hz, 1H, H-6eq). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.6, 166.0, 155.8, 139.01, 122.5, 111.6, 89.8, 80.0, 65.9, 52.6, 41.4, 41.1, 28.3, 24.1, 23.9, 18.9. IR (ATR, cm^{-1}): ν 3418 (OH st), 2938, 2871, 1737 (C═O st), 1670 (C═O st), 1641, 1405, 1280, 849, 749. HRMS (ESI+) *m*/*z*: calcd for $C_{18}H_{25}NO_5Na$ 358.1625 (MNa^+); found 358.1620. $[\alpha]_D$ −71.9 (*c* 2.3, $CHCl_3$).

(2*R*,6′*S*,7a′*R*)-*tert*-Butyl-2-(6-hydroxy-2-oxo-7,7a-dihydro-2*H*-benzofuran-7a-yl)piperidin-1-carboxylate (19). The same experimental procedure previously described for the preparation of (−)-**19** was followed, starting with 488 mg (0.85 mmol) of (+)-**18** and yielding (+)-**19** (247 mg, 0.74 mmol, 87%) as a colorless oil. $[\alpha]_D$ +72.3 (*c* 2.8, $CHCl_3$).

Allosecurinine. To a solution of (−)-**19** (90 mg, 0.268 mmol) in dry CH_2Cl_2, under nitrogen atmosphere at 0 °C, Et_3N (94 μL, 0.671 mmol) was added. After 10 min, MsCl (31 μL, 0.399 mmol) was added, and the reaction mixture was allowed to stir at 0 °C for 30 min. The mixture was quenched with NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo, affording an oil identified as the corresponding mesylate derivative. The previous crude material was dissolved in CH_2Cl_2, and TFA (83 μL, 1.067 mmol) was added. The mixture was allowed to stir for 3 h at room temperature and concentrated under reduced pressure. The resulting crude material was dissolved in THF (3 mL) and aqueous K_2CO_3 saturated solution (1 mL). The mixture was allowed to stir for 30 min at room temperature, diluted with brine (4 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by flash chromatography using a flash chromatographic system with a basic alumina presealed column and *n*-hexane/AcOEt (8:1 to 1:1) as eluent, yielding allosecurinine, **2** (40.5 mg, 0.186 mmol, 69%) as a yellowish solid. Mp: 126−127 °C (ethyl ether) {lit. 136−138 °C,[20] 137−138 °C,[21] 136−138 °C,[22] 128 °C (ether)[23]}. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 6.82 (dd, *J* = 9.1, 5.3 Hz, 1H, H-15), 6.63 (dd, *J* = 9.1, 0.9 Hz, 1H, H-14), 5.68 (s, 1H, H-12), 3.85 (t, *J* = 4.9 Hz, 1H, H-7), 3.60 (dd, *J* = 13.1, 3.5 Hz, 1H, H-2), 2.81−2.68 (m, 2H, 2H-6), 2.61 (dd, *J* = 9.6, 4.4 Hz, 1H, H-8), 1.89 (d, *J* = 9.7 Hz, 1H: H-8), 1.73−1.56 (m, 3H: 2H-5, H-4), 1.46−1.33 (m, 1H, H-4), 1.33−1.24 (m, 1H, H-3eq), 1.15 (qd, *J* = 13.1, 6.0 Hz, 1H: H-3ax). ^{13}C NMR (150 MHz, CD_2Cl_2): δ 172.1, 167.4, 148.7, 122.1, 108.3, 91.4, 60.5, 58.5, 43.4, 42.4, 22.1, 20.9, 18.5. IR (ATR, cm^{-1}): ν 2936, 2855, 1742 (C═O st), 1623, 1454, 1250, 1053, 961, 690. HRMS (ESI+) *m*/*z*: calcd for $C_{13}H_{15}NO_2H$ 218.1176 (MH^+); found 218.1180. $[\alpha]_D$ −1092 (*c* 1.0, EtOH) {lit. $[\alpha]_D$ −1082 (EtOH),[20] $[\alpha]_D$ −1004 (MeOH),[21] $[\alpha]_D$ −1082 (EtOH),[22] $[\alpha]_D$ −1140[23]}.

Viroallosecurinine. The same experimental procedure previously described for the preparation of allosecurinine, **2**, was followed, starting with 110 mg (0.328 mmol) of (+)-**19** and affording

viroallosecurinine (48 mg, 0.221 mmol, 67%) as a yellowish solid. Mp: 138−139 °C (*n*-hexane/acetone) {lit. 133−134 °C (ligroine),[25] 135−136 °C,[26] 145−147 °C (*n*-hexane/acetone)[16j]}. $[\alpha]_D$ +1068 (*c* 1.2, EtOH) {$[\alpha]_D$ +1084.6 (EtOH),[24] $[\alpha]_D$ +1200 (EtOH),[25] $[\alpha]_D$ +990 (*c* 0.98, EtOH),[26] $[\alpha]_D$ +1113 (*c* 1.0, EtOH)[16j]}.

Acknowledgment. We acknowledge financial support from DGI (project CTQ2004-2539). G.G.B. and M.C. thank DURSI and FSE for a predoctoral grant. We also acknowledge MCYT-ERDF for a Ramón y Cajal contract (F.B.).

Supporting Information Available: General experimental data. Copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801470U