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Applications of vinylogous Mannich reactions. Total synthesis of the angiotensin converting enzyme inhibitor (−)-A58365A

Andreas Reichelt, Scott K. Bur and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, TX 78712, USA

Dedicated to Professor Yoshito Kishi in recognition of his many contributions to organic chemistry and his receipt of the Tetrahedron Prize

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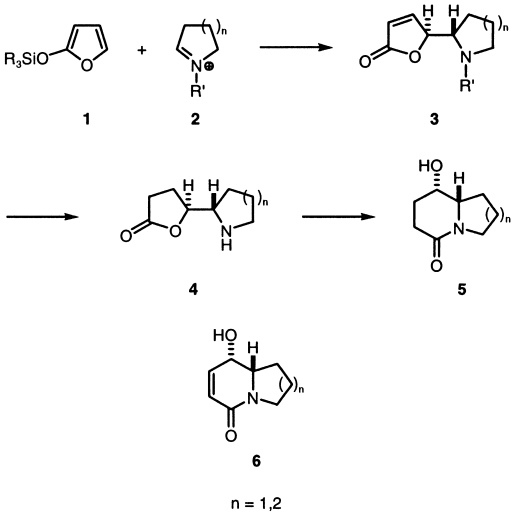
Abstract—A concise enantiospecific synthesis of the angiotensin converting enzyme inhibitor (−)-A58365A (**7**) has been achieved following a strategy in which a vinylogous Mannich reaction and a lactone–lactam rearrangement served as the key transformations. The trimethylsilyloxyfuran derived from **25**, which was prepared from the known sulfoxide **16**, served as the nucleophilic partner in a vinylogous Mannich reaction with the chiral *N*-acyliminium ion that was generated in situ from the aminal **26**. Addition of a further quantity of TMSOTf cleaved the *N*-Boc group from the adducts **27** to give a mixture of diastereomeric amino butenolides **28**. Treatment of this mixture with LiOMe/MeOH furnished **10**, and acid-catalyzed hydrolysis of the methyl ester groups delivered (−)-A58365A in 37% overall yield over the longest linear sequence of eight steps.

1. Introduction

The design and development of general and efficient strategies for alkaloid synthesis has long been an important objective in our laboratories. It is perhaps a truism that one cannot long engage in alkaloid synthesis without encountering the Mannich reaction, a transformation that plays a central role in the biogenesis of these natural products. Indeed, the venerable Mannich reaction and its variants represent one of the more powerful constructs for alkaloid synthesis.[1] A number of years ago we became interested in the vinylog of the Mannich reaction as a tool for the rapid assembly of skeletal frameworks commonly found in alkaloid natural products. We have since employed various types of vinylogous Mannich reactions as key steps in executing concise syntheses of a number of alkaloids.[2]

Numerous combinations of linear and cyclic dienols and iminium ions may participate in vinylogous Mannich additions to produce substituted δ-amino-α,β-unsaturated carbonyl compounds, which are highly versatile intermediates in alkaloid synthesis. However, we have been particularly interested in one useful version of this bond construction that is illustrated by the sequence of transformations depicted in Scheme 1. When trialkylsilyloxyfurans **1** add to cyclic iminium ions **2**, two diastereomeric aminoalkyl butenolides are produced with **3** typically being the major adduct.[2b,3] Significantly, butenolides **3** and their saturated



Scheme 1.

counterparts **4** are structural arrays that are found in a number of alkaloids. Moreover, compounds related to **4** were known to undergo facile lactone–lactam rearrangements to generate the indolizidine (n=1) or quinolizidine (n=2) ring systems **5** that are common to many biologically important alkaloids.[2c,4] Although the transformation of butenolides like **3** to the bicyclic unsaturated lactams **6** is unknown, related reorganizations have been reported.[2d,5] It is noteworthy that others have recognized the importance of this variant of the vinylogous Mannich reaction for the syntheses of alkaloids[4b,c,e,6] peptidomimetics,[4d] and other biologically active compounds.[4f,7]

Keywords: vinylogous Mannich reaction; enantioselection; lactone–lactam rearrangement.

* Corresponding author. Tel.: +1-512-471-3915; fax: +1-512-471-4180; e-mail: sfmartin@mail.utexas.edu

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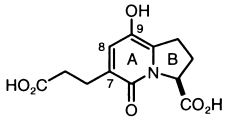
Because of our interest in developing new applications of the vinylogous Mannich reaction, we were attracted to the hydroxy indolizidine (−)-A58365A (**7**) as a potential target. (−)-A58365A and its homolog A58365B (**8**) were isolated from the fermentation broth of the soil bacterium *Streptomyces chromofuscus* NRRL 15089 by researchers at Lilly Research Laboratories and were found to be potent angiotensin converting enzyme inhibitors effective at nanomolar concentrations.[8] Despite the appearance of four different syntheses of **7**,[9–12] we envisioned that this compound might be more readily prepared by deploying a Mannich-based strategy.



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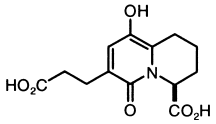

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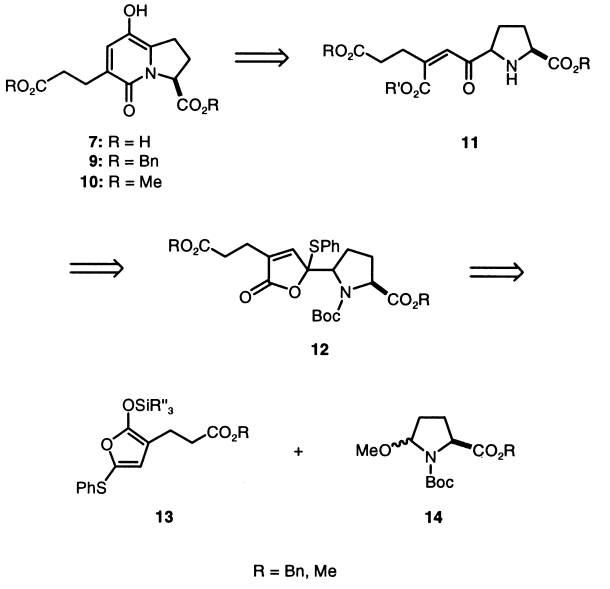
In developing the plan for the synthesis of **7** that is outlined in Scheme 2, we benefited in several important ways from the elegant work of our predecessors. The last step in several syntheses of **7** involved hydrogenolysis of the dibenzyl diester **9**,[9,12] and although the corresponding dimethyl ester **10** had been prepared, it had not been directly transformed into **7**.[9,10] Hence, the initial target of our endeavors was **9**. It was also known that introduction of the C(7)–C(8) double bond by oxidation was fraught with difficulty as the B ring was prone to undergo facile concomitant oxidation, thereby resulting in reduced yields of the desired product.[10,11b] It would thus be optimal if the hydroxy pyridone A ring were generated directly in the correct oxidation state.

Based upon the foregoing discussion, we envisioned that the vinylogous Mannich adduct **12** (R=Bn) would be an ideal precursor of **9**. Removal of the nitrogen protecting group from **12** and opening of the butenolide ring was anticipated to proceed with spontaneous loss of thiophenoxide to generate **11**, which would then undergo cyclization to **9**.

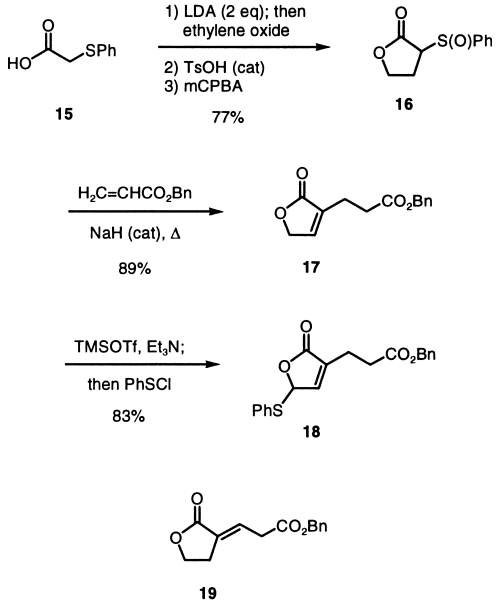


Scheme 2.

Inasmuch as there are no stereogenic centers in the A ring of **7**, the stereoselectivity of the reaction between **13** and **14** to give **12** was irrelevant. We had considerable experience with vinylogous Mannich reactions involving substrates related to **13** and **14** and were thus confident of the viability of this addition. However, we anticipated that the subsequent conversion of **12** into **9** via **11** or a related intermediate might prove somewhat more challenging as we had previously experienced difficulties with lactone–lactam rearrangements of butenolide derivatives.[2d] It should not escape notice that application of this same plan to the piperidine analogue of **14** would provide access to (−)-A58365B (**8**).

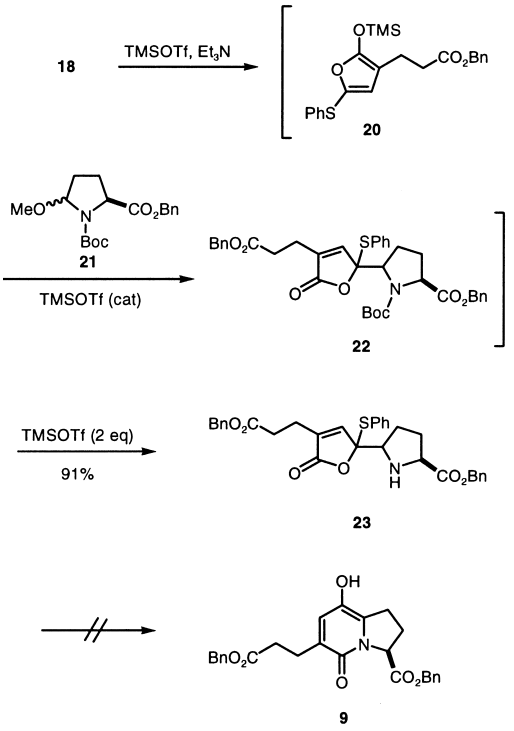
2. Results and discussion

The synthesis of (−)-A58365A (**7**) commenced with the conversion of commercially available thiophenylacetic acid (**15**) into the known sulfoxide **16** in 77% yield according to published procedures.[13] Base-induced Michael addition of **16** to benzyl acrylate and subsequent sulfoxide elimination afforded an inseparable mixture (ca. 12:1) of the desired butenolide **17** together with its *exo*-isomer **19** in 89% combined yield. Treatment of this mixture with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of Et_3N generated an intermediate trimethylsilyloxyfuran that was then allowed to react in situ with freshly prepared benzenesulfenyl chloride[14] to provide the desired butenolide **18** in 83% overall yield (Scheme 3).



Scheme 3.

The stage was now set for the key vinylogous Mannich reaction. In the event, **18** was first treated with TMSOTf in the presence of base to generate the intermediate silyloxyfuran **20** (Scheme 4). The known aminal **21**[15] and an additional portion of TMSOTf were then added, and the reaction was allowed to proceed at −78°C to give a mixture of adducts **22**. These compounds were not isolated, but rather excess TMSOTf was simply added to the reaction to effect



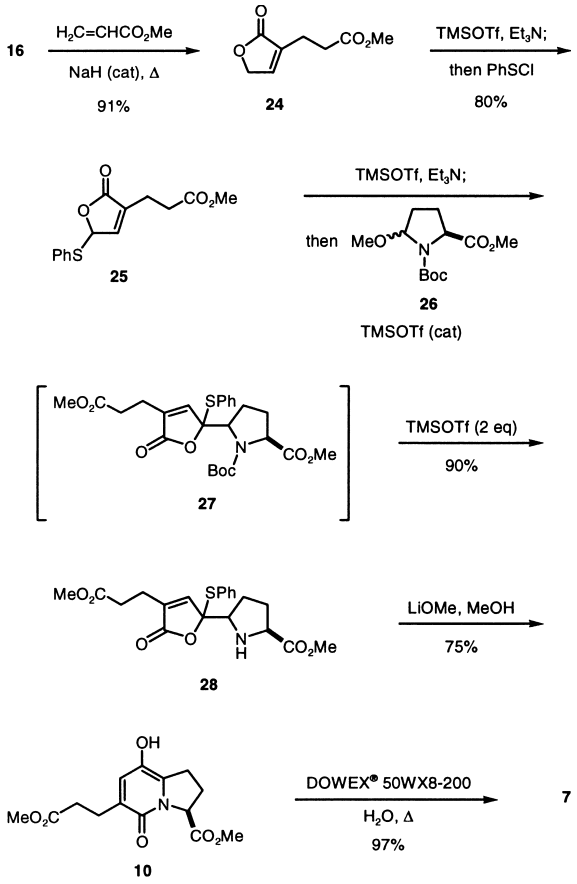
Scheme 4.

the removal of the *N*-Boc protecting group, thereby furnishing **23** in 91% yield from **18** as a mixture of four diastereomers (*ca.* 46:43:6:5).[16] Inasmuch as this mixture would converge to a single compound in the subsequent lactone–lactam rearrangement, the diastereomers were not individually isolated and characterized.

Thus far our plan had proceeded smoothly according to our expectations. We were therefore ill-prepared for the troubles that followed. Despite rather extensive experimentation, we were unable to effect the requisite reorganization of **23** into **9**. Initial experiments to induce the lactone–lactam rearrangement directly by heating **23** in DMF or toluene were unsuccessful.[2c,4a–c] We then examined the feasibility of using various nucleophiles such as benzyloxide, cyanide,[17] azide,[18] or a methyl toluenesulfonamide–DBU system[2d,19] in different solvents. Each of these reagents would have been anticipated to open the lactone ring to give an acyclic intermediate of the form **11** that would then cyclize to **9**. Under mild conditions, starting material was invariably recovered from all of these experiments, whereas under more forcing conditions, mixtures of unidentified products were obtained. Attempted activation of the secondary amine nitrogen with Me_3Al or Me_2AlCl according to the Weinreb protocol also led to the formation of complex mixtures.[20]

We and others had previously found that aminoalkyl butyrolactones may undergo facile lactone–lactam rearrangement in the presence of methoxide in methanol.[2c,4] However, use of these conditions to promote the conversion of **23**, which was in fact a mixture of four different stereoisomers, into **9** would have been complicated by transesterification of the benzyl esters in both **23** and **9**. The occurrence of such side reactions would render monitoring of the reaction progress more difficult. Because **23** was in short supply at that time, we therefore decided to prepare the corresponding dimethyl ester **28** following the same procedures used to obtain **23** (Scheme 5). Accordingly, sulfoxide **16** was first transformed into the butenolide **25** in 73% overall yield. When the trimethylsilyloxyfuran prepared in situ from **25** was allowed to react with the known aminal **26**[21] in the presence of TMSOTf, the expected vinylogous Mannich reaction ensued to generate **27**, deprotection of which furnished **28** as a mixture (ca. 53:41:4:2)[16] of stereoisomeric adducts. We were delighted to discover that treatment of **28** with lithium methoxide in MeOH induced the desired lactone–lactam rearrangement to deliver **10** in 75% yield.

At this stage, we briefly considered the possibility of converting **10** into **9** in order to intersect with Danishefsky's synthesis of **7**.[9] However, we were also intrigued by the more attractive possibility of transforming **10** directly into **7**. Indeed, heating an aqueous solution of **10** under reflux in the presence of DOWEX® 50WX8-200 ion-exchange resin furnished (−)-A58365A (**7**) in 97% yield.



Scheme 5.

This concise enantiospecific synthesis of (−)-A58365A (**7**) clearly exemplifies the utility of the vinylogous Mannich reaction followed by lactone–lactam rearrangement as a powerful strategy for alkaloid synthesis. Systematic optimization of the reaction sequence allowed us to incorporate multiple steps into one-pot operations, thereby providing **7** in 37% overall yield in a longest linear sequence of only

eight steps from commercially available starting materials. The synthesis is readily scalable to prepare gram quantities of **7**. Further applications of vinylogous Mannich reactions to problems in alkaloid synthesis are the subject of current investigations in our laboratories, and the results of these will be reported in due course.

3. Experimental

3.1. General

Unless otherwise noted, solvents and reagents were reagent-grade and were used without further purification. Tetrahydrofuran (THF) and ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (MeOH) was dried by passage through two columns of activated molecular sieves. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride, whereas benzene was distilled from sodium. Triethylamine (Et_3N) was distilled from CaH_2. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been oven or flame dried. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM) according to Still's protocol,[22] eluting with solvents as indicated. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard Me_4Si (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and app, apparent. Infrared (IR) spectra were recorded either neat on sodium chloride plates or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. Percent yields are given for compounds that were ≥95% pure as judged by NMR.

3.1.1. 3-(2-Oxo-2,5-dihydrofuran-3-yl)propionic acid methyl ester (24). Sodium hydride (37 mg of a 60% suspension in paraffin oil, 0.98 mmol) was added to a solution of **16**[13] (985 mg, 4.68 mmol) in THF (47 mL), and the mixture was stirred at room temperature for 15 min. Freshly distilled methyl acrylate (1.27 mL, 14.05 mmol) was added, and the mixture was stirred at room temperature for 1 h and then at 50°C for 2 h. The mixture was cooled to room temperature and partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (6 mL). The aqueous layer was extracted with EtOAc (2×50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to give 723 mg (91%) of an inseparable mixture (12:1) of **24** and its exocyclic double bond isomer as a colorless oil; ^1H NMR δ 7.16 (t, J=1.6 Hz, 0.92H), 6.86–6.81 (m, 0.08H), 4.72 (d, J=1.6 Hz, 1.84H), 4.36 (t, J=7.4 Hz, 0.16H), 3.69 (s, 0.24H), 3.64 (s, 2.76H), 3.20 (dt, J=7.4, 1.8 Hz, 0.16H), 2.89–2.84 (m, 0.16H), 2.60–2.58 (comp, 3.68H); ^{13}C NMR for major isomer: δ 173.8, 172.6, 145.4, 132.5, 70.1, 51.7, 31.5, 20.8; for minor isomer: δ 170.3, 169.7, 131.0, 128.6, 65.2, 52.2, 35.3, 25.1; IR (neat) ν 1775, 1732, 1439, 1207, 1169, 1082, 1056 cm^{-1}; MS (CI+) m/z 171.0653 ($C_8H_{10}O_4$+H requires 171.0657), 139 (base).

3.1.2. 3-(2-Oxo-2,5-dihydrofuran-3-yl)propionic acid benzyl ester (17). Prepared analogously from **16**[13] and benzyl acrylate in 89% yield as a pale yellow solid and an inseparable mixture (12:1) of **17** and **19**; mp 48–51°C; ^1H NMR δ 7.34–7.27 (comp, 5H), 7.06 (t, J=1.8 Hz, 0.92H), 6.88–6.84 (m, 0.08H), 5.12 (s, 0.16H), 5.09 (s, 1.84H), 4.65 (d, J=1.8 Hz, 1.84H), 4.33 (t, J=7.3 Hz, 0.16H), 3.24 (dt, J=7.4, 1.8 Hz, 0.16H), 2.85–2.81 (m, 0.16H), 2.63–2.61 (comp, 3.68H); ^{13}C NMR for major isomer: δ 173.7, 171.9, 145.4, 135.7, 132.2, 128.4, 128.3, 128.2, 70.0, 66.3, 31.6, 20.7; for minor isomer: δ 170.2, 169.0, 135.2, 130.8, 128.7, 128.5, 128.4, 128.3, 66.9, 65.2, 35.4, 25.1; IR ($CHCl_3$) ν 1749, 1260, 1228, 1204, 1162, 1081, 1057, 831 cm^{-1}; MS (CI+) m/z 247.0971 ($C_{14}H_{14}O_4$+H requires 247.0970) (base), 139.

3.1.3. 3-(2-Oxo-5-phenylthio-2,5-dihydrofuran-3-yl)propionic acid methyl ester (25). Freshly distilled TMSOTf (697 μL, 3.85 mmol) was added to a mixture of **24** and its isomer prepared above (596 mg, 3.50 mmol) and Et_3N (586 μL, 4.20 mmol) in CH_2Cl_2 (35 mL) at 0°C, and the reaction was stirred at 0°C for 1 h. The mixture was cooled to −78°C, and a solution containing freshly prepared benzenesulfenyl chloride [from thiophenol (450 μL, 4.38 mmol) and *N*-chlorosuccinimide (702 mg, 5.25 mmol) in CH_2Cl_2 (5 mL)][14] was added. The mixture was stirred at −78°C for 0.5 h and then poured into saturated aqueous $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography eluting with EtOAc/hexanes (1:1) to give 777 mg (80%) of **25** as a pale yellow oil; ^1H NMR δ 7.49–7.46 (m, 2H), 7.35–7.28 (comp, 3H), 6.96 (app q, J=1.6 Hz, 1H), 6.09 (app q, J=1.6 Hz, 1H), 3.64 (s, 3H), 2.49–2.40 (comp, 3H), 2.31–2.25 (m, 1H); ^{13}C NMR δ 172.4, 171.8, 145.50, 134.5, 134.4, 129.3, 129.2, 129.1, 85.5, 51.8, 31.3, 20.4; IR (neat) ν 1770, 1731, 1440, 1202, 1170, 1044, 943, 750, 692 cm^{-1}; MS (CI+) m/z 279.0694 ($C_{14}H_{14}O_4S$+H requires 279.0691) (base), 247, 169.

3.1.4. 3-(2-Oxo-5-phenylthio-2,5-dihydrofuran-3-yl)propionic acid benzyl ester (18). Prepared analogously from the mixture of **17** and **19** prepared above in 83% yield as a pale yellow oil; ^1H NMR δ 7.47–7.45 (m, 2H), 7.37–7.28 (comp, 8H), 6.90 (app q, J=1.6 Hz, 1H), 6.02 (app q, J=1.6 Hz, 1H), (app d, J=2.0 Hz, 2H), 2.55–2.42 (comp, 3H), 2.37–2.30 (m, 1H); ^{13}C NMR δ 171.8, 171.7, 145.6, 135.7, 134.5, 134.4, 129.4, 129.2, 129.1, 128.6, 128.4, 128.3, 85.5, 66.5, 31.6, 20.4; IR (neat) ν 1770, 1732, 1440, 1292, 1161, 1046, 943, 748, 695 cm^{-1}; MS (CI+) m/z 355.1004 ($C_{20}H_{18}O_4S$+H requires 355.1004) (base), 201.

3.1.5. 5-[4-(2-Methoxycarbonylethyl)-5-oxo-2-phenythio-2,5-dihydrofuran-2-yl]pyrrolidine-2-carboxylic acid methyl esters (28). Freshly distilled TMSOTf (461 μL, 2.55 mmol) was added to a mixture of **25** (644 mg,

2.31 mmol) and Et_3N (387 μL, 2.78 mmol) in CH_2Cl_2 (23 mL) at 0°C. The mixture was stirred at 0°C for 1 h and then cooled to −78°C. A solution of **26**[21] (660 mg, 2.55 mmol) in CH_2Cl_2 (3 mL) and then TMSOTf (84 μL, 0.463 mmol) were added, and the reaction mixture was stirred at −78°C for 1 h. Another quantity of TMSOTf (838 μL, 4.63 mmol) was then added. The cooling bath was exchanged for an ice bath, and the mixture was stirred at 0°C for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ (30 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2×30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography eluting with EtOAc/hexanes (2:1) to give 839 mg (90%) of a mixture (53:41:4:2) of four diastereomers of **28** as a colorless oil. For spectroscopic characterization an inseparable mixture (53:41) of the two major isomers was also isolated by chromatography; ^{1}H NMR δ 7.43–7.40 (comp, 2H), 7.35–7.32 (comp, 1H), 7.29–7.25 (comp, 2H), 6.83 (t, *J*=1.4 Hz, 0.56H), 6.81 (t, *J*=1.4 Hz, 0.44H), 3.86–3.81 (comp, 2H), 3.70 (s, 1.32H), 3.69 (s, 1.68H), 3.63 (s, 1.32H), 3.62 (s, 1.68H), 2.35–2.22 (comp, 3H), 2.20–2.13 (comp, 1H), 2.02–1.80 (comp, 4H); ^{13}C NMR for major isomer: δ 175.4, 172.4, 171.5, 148.3, 137.1, 133.9, 129.8, 129.0, 128.1, 98.6, 62.1, 60.0, 52.2, 51.7, 31.4, 29.7, 26.6, 20.1; for minor isomer: δ 175.3, 172.4, 171.4, 148.0, 137.3, 137.1, 133.8, 129.8, 128.9, 127.9, 98.4, 62.4, 60.1, 51.7, 31.4, 30.0, 27.0, 20.0; IR (neat) ν 3357, 1770, 1748, 1734, 1716, 1434, 1208, 1026, 753, 694 cm^{-1}; MS (CI+) *m/z* 406.1323 ($C_{20}H_{23}NO_6S$+H requires 406.1324) (base), 296.

3.1.6. 5-[4-(2-Benzyloxycarbonylethyl)-5-oxo-2-phenythio-2,5-dihydrofuran-2-yl]pyrrolidine-2-carboxylic acid benzyl esters (23). Prepared analogously from **18** and **21**[15] in 91% yield as a mixture (46:43:6:5) of four diastereomers and as a colorless oil. For spectroscopic characterization an inseparable mixture (46:43) of the two major isomers was isolated by chromatography; ^{1}H NMR δ 7.41–7.38 (comp, 2H), 7.37–7.29 (comp, 11H), 7.26–7.22 (comp, 2H), 6.79 (t, *J*=1.2 Hz, 0.52H), 6.76 (t, *J*=1.2 Hz, 0.48H), 5.12 (br s, 2H), 5.06 (br d, *J*=2.4 Hz, 2H), 3.88–3.80 (comp, 2H), 2.37–2.22 (comp, 3H), 2.18–2.11 (comp, 1H), 2.09–2.01 (comp, 1H), 1.94–1.78 (comp, 3H); ^{13}C NMR for major isomer: δ 174.9, 171.7, 171.5, 148.3, 137.1, 135.7, 135.5, 133.8, 129.7, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 98.6, 66.8, 66.4, 62.0, 60.1, 31.6, 29.7, 26.6, 20.1; for minor isomer: δ 174.7, 171.8, 171.3, 148.0, 137.3, 135.7, 135.5, 133.7, 129.7, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 98.4, 66.8, 66.4, 62.3, 60.2, 31.6, 30.0, 26.9, 20.0; IR (neat) ν 3355, 1770, 1738, 1732, 1715, 1455, 1440, 1162, 1026, 749, 696 cm^{-1}; MS (CI+) *m/z* 558.1953 ($C_{32}H_{31}NO_6S$+H requires 558.1950) (base), 448, 407, 355, 294.

3.1.7. (3*S*)-8-Hydroxy-6-(2-methoxycarbonylethyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic acid methyl ester (10). A solution of freshly prepared 1 M methanolic lithium methoxide (2.91 mL, 2.91 mmol) was added to a solution of **28** (785 mg, 1.94 mmol) in MeOH (20 mL), and the mixture was stirred at room temperature for 14 h. AcOH (0.2 mL) was added and the mixture was concentrated in vacuo. The resulting brown oil was purified by flash chromatography eluting with CH_2Cl_2/MeOH (19:1) to give 419 (75%) of **22** as a off-white foam; ^{1}H NMR δ 7.22 (s, 1H), 5.11 (dd, *J*=9.4, 3.2 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.14 (ddd, *J*=17.1, 9.2, 3.9 Hz, 1H), 3.07 (dd, *J*=17.1, 8.6 Hz, 1H), 2.84–2.71 (m, 2H), 2.59 (br t, *J*=7.3 Hz, 2H), 2.54–2.46 (m, 1H), 2.31–2.25 (m, 1H); ^{13}C NMR δ 173.6, 170.7, 158.8, 135.4, 133.9, 132.3, 128.5, 62.2, 52.7, 51.6, 32.6, 27.2, 26.8, 25.9; IR (neat) ν 3165 (br), 1738, 1548, 1437, 1362, 1286, 1207, 1179 cm^{-1}; MS (CI+) *m/z* 296.1139 ($C_{14}H_{17}NO_6$+H requires 296.1134) (base), 264; $[\alpha]_D^{26}$=−195.1° (*c* 1.5, CH_2Cl_2); lit. $[\alpha]_D^{25}$=−184.8° (*c* 1.5, CH_2Cl_2).[9] $[\alpha]_D^{21}$=−169.6° (*c* 1.5, CH_2Cl_2).[10]

3.1.8. (−)-A58365A (7). A solution of **10** (135 mg, 0.457 mmol) in H_2O (5 mL) containing DOWEX® 50WX8-200 ion-exchange resin (135 mg) was heated under reflux for 3 h. Norit® SA3-100 (70 mg) was added, and the mixture was heated under reflux for another 10 min. The solids were removed by filtration and then washed with H_2O (2×5 mL). The combined aqueous filtrates were washed with CH_2Cl_2 (2×10 mL) and concentrated in vacuo to give 118 mg (97%) of **7** as a white foam; ^{1}H NMR (D_2O) δ 7.24 (s, 1H), 5.06 (dd, *J*=10.0, 3.4 Hz, 1H), 3.07 (ddd, *J*=17.3, 9.5, 3.8 Hz, 1H), 3.00 (dd, *J*=17.3, 8.8 Hz, 1H), 2.70–2.61 (m, 2H), 2.58–2.49 (comp, 3H), 2.33–2.27 (m, 1H); ^{13}C NMR δ 177.7, 174.2, 159.4, 135.6, 134.9, 134.3, 128.0, 63.3, 32.7, 27.2, 26.3, 25.2; IR (neat) ν 3192 (br), 1714, 1530, 1440, 1410, 1284, 1209 cm^{-1}; MS (FAB+) *m/z* 268.0817 ($C_{12}H_{13}NO_6$+H requires 268.0821) (base), 250, 241, 208; $[\alpha]_D^{26}$=−196.3° (*c* 1.0, H_2O); lit. $[\alpha]_D^{25}$=−199.5° (*c* 1.0, H_2O),[8c] $[\alpha]_D^{25}$=−190.5° (*c* 0.1, H_2O).[9]

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References

1. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1045–1070. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929–1972. (c) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242.
2. (a) Martin, S. F.; Hunter, J. E.; Benage, B.; Geraci, L. S.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161–6171. (b) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990–6997. (c) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905–8914. (d) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918–5924. (e) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003–8010.
3. de Oliveira, M. d. C. V. F.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995–6997.
4. (a) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1985**, 31–34. (b) Morimoto, Y.; Nishida, K.; Hayashi, Y.;

Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773–5776. (c) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221–1222. (d) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567–1572. (e) Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquotti, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395–1400. (f) Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999–7001.

5. Rebek, Jr., J.; Tai, D. F.; Shue, Y. K. *J. Am. Chem. Soc.* **1984**, *106*, 1813–1819.
6. Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *J. Org. Lett.* **2001**, *3*, 2505–2508.
7. Pichon, M.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **1999**, *40*, 8567–8570.
8. (a) O'Connor, S.; Somers, P. *J. Antibiot.* **1985**, *38*, 993–996. (b) Nakatsukasa, W. M.; Wilgus, R. M.; Thomas, D. N.; Mertz, F. P.; Boeck, L. D. *J. Antibiot.* **1985**, *38*, 997–1002. (c) Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Du Bus, R. H.; Baker, P. J. *J. Antibiot.* **1985**, *38*, 1003–1007. (d) Hunt, A. H.; Mynderse, J. S.; Samlaska, S. K.; Fukuda, D. S.; Maciak, G. M.; Kirst, H. A.; Occolowitz, J. L.; Swartzendruber, J. K.; Jones, N. D. *J. Antibiot.* **1988**, *41*, 771–779.
9. Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1989**, *30*, 3621–3624.
10. (a) Moeller, K. D.; Wong, P. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 739–742. (b) Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434–11445.
11. (a) Clive, D. L. J.; Coltart, D. M. *Tetrahedron Lett.* **1998**, *39*, 2519–2522. (b) Clive, D. L. J.; Coltart, D. M.; Zhou, Y. *J. Org. Chem.* **1999**, *64*, 1447–1454.
12. (a) Straub, C. S.; Padwa, A. *Org. Lett.* **1999**, *1*, 83–85. (b) Padwa, A.; Sheehan, S. M.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 8648–8659.
13. Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn* **1977**, *50*, 242–247.
14. Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208–1217.
15. Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706–9707.
16. The ratio was determined by integration of the ^{1}H NMR signals of the vinylic protons.
17. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033–2036.
18. Gómez-Vidal, J. A.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2481–2484.
19. Drummond, J. T.; Johnson, G. *Tetrahedron Lett.* **1988**, *29*, 1653–1656.
20. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171–4174. (b) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685–2688.
21. Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789–4792.
22. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.