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# A Maillard Approach to 2-Formylpyrroles: Synthesis of Magnolamide, Lobechine and Funebral

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A convenient synthesis of the traditional medicine constituents magnolamide, lobechine and funebral is described. Construction of the 2-formylpyrrole core of these natural products was achieved by means of a Maillard reaction, involving condensation of the sugar surrogate, dihydropyranone **9**, with the requisite primary amines. This approach offers a very direct and general route to the 2-formylpyrrole ring system.

## Introduction

The 2-formylpyrrole motif is featured in a number of natural products with a broad spectrum of biological activities (Figure 1). Although little studied, numerous members of this class of compounds are routinely used as folk medicinal remedies around the world.[1–5] In a continuation of our efforts toward the preparation of diverse 2-formylpyrrole derivatives, we became interested in the total synthesis of magnolamide (**1**), lobechine (**2**), and funebral (**3**). Magnolamide (**1**), a putrescine alkaloid, was first isolated from the leaves of *Magnolia coco* in 1998 and has since been found to inhibit $CuSO_4$-induced oxidation of human low-density lipoprotein ($IC_{50} = 9.7 \pm 2.8$ μM).[1,6] Lobechine (**2**) was isolated from the culture medium of the plant *Lobelia chinenesis*, which exhibited moderate anti-inflammatory activity by inhibition of elastase release ($IC_{50} = 25.0 \pm 7.0$ μM).[2] Funebral (**3**), a unique pyrrole lactone alkaloid with three contiguous stereogenic centers, was isolated in 1984 from the flowers of *Quararibea funebris*.[2]

To date, several total syntheses of magnolamide **1** and funebral **3** have been reported, but no synthetic studies of lobechine **2** have been forthcoming.[6–10] To the best of our knowledge, methodologies currently in use to assemble the 2-formylpyrrole core of these natural products and other related compounds rely on direct *N*-alkylation of pyrrole-containing building blocks or pyrrole formation through the classical Paal–Knorr approach. However, such syntheses often require lengthy protection/deprotection sequences and oxidation state manipulations to achieve desymmetrization of the pyrrole core. In an attempt to circumvent these drawbacks, a modified Maillard reaction[11] was adapted by our group to access differentially substituted pyrroles from a dihydropyranone precursor. As an illustration of these strategies, we recently disclosed the syntheses of acortatarin A (**4**) and the free amino acid form of pyrraline **5**.[12,13] Herein, we describe the syntheses of magnolamide (**1**), lobechine (**2**), and funebral (**3**).

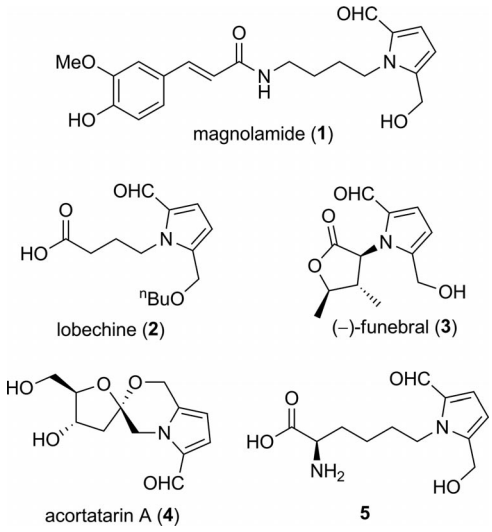


Figure 1. 2-Formylpyrrole natural products.

## Results and Discussion

Retrosynthetically, magnolamide (**1**) was envisioned to derive from peptide coupling of ferulic acid **6** to 2-formylpyrrole **7** (Scheme 1). A Maillard type disconnection of **7** in turn leads to condensation partners **8** and dihydropyranone **9**. Similarly, amines **10** and **11a** serve as precursors for the syntheses of lobechine **2** and funebral **3**, respectively.

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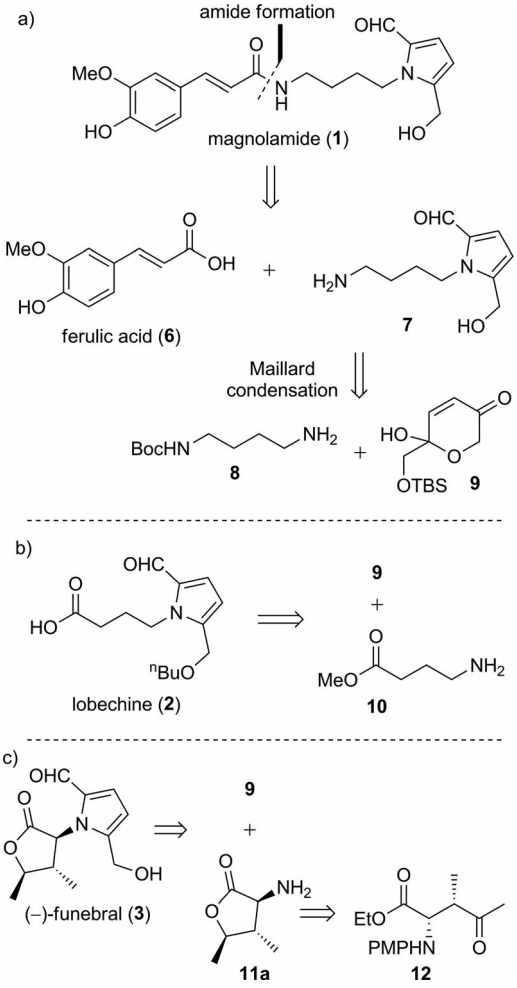
A survey of the literature revealed that the shortest total stereoselective synthesis of amino lactone **11a** or its corresponding hydrochloride salt required ten linear steps from commercially available starting materials,[9,10,14–16] thus making our first challenge an efficient preparation of amino lactone **11a**. Building on Mioskowski's work,[14] we envisioned a facile route to **11a** through asymmetric reduction of known ketone **12**.[17]

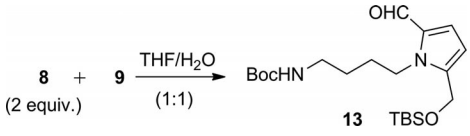



Scheme 1. Retrosynthetic analysis of 2-formylpyrrole-containing natural products (a) magnolamide (**1**), (b) lobechine (**2**), and (c) (–)-funebral (**3**).

Our synthetic efforts began with the key Maillard condensation between commercially available amine **8** and known dihydropyranone **9**.[12] The Maillard reaction,[18,19] or nonenzymatic browning, represents a host of complex reactions that can occur between primary amines and sugar derivatives upon heating. Possible Maillard products include, but are not limited to, pyridines, pyrazines, imidazoles, and pyrroles.[20] Nevertheless, based on our previous studies, we were optimistic that the use of excess amine in conjunction with careful control of the reaction pH, time and temperature, would allow selective formation of the desired 2-formylpyrrole adducts.

An initial screen of conditions for coupling of **8** and **9** revealed pH dependence of the Maillard reaction (Table 1). At pH > 8 (entry 1), only unreacted starting materials were detected, whereas cleavage of the TBS protecting group of dihydropyranone **9** was observed at pH < 5 (entry 2), effectively reducing the reactivity of **9** towards amine **8**. Pleasingly, the desired pyrrole **13** could be obtained as the sole product when the reaction was carried out in the range of pH 5–8, with pH 5 being the optimum value (entry 3). Furthermore, it was found that increasing the reaction temperature to 60 °C significantly promoted the coupling and reduced the reaction time by half (entry 4). The use of temperatures above 60 °C led to decomposition of the reaction mixture (entry 5).

Table 1. Examination of conditions for the Maillard coupling of **8** to **9**.




| Entry | pH | Temp. [°C] | Time [h] | Yield [%] |
|---|---|---|---|---|
| 1 | >8 | 40 | 16 | 0[a] |
| 2 | <5 | 40 | 16 | 0[b] |
| 3 | 5 | 40 | 16 | 57 |
| 4 | 5 | 60 | 8 | 60 |
| 5 | 5 | 70 | 8 | 0[c] |

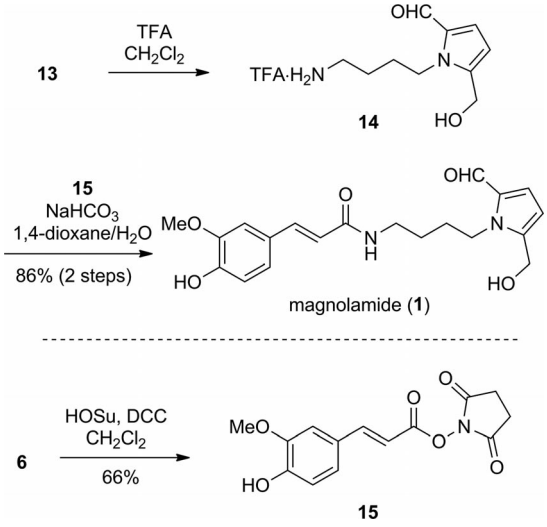
[a] Unreacted **9** recovered. [b] Deprotected **9** isolated. [c] Decomposition.

Treatment of pyrrole **13** with trifluoroacetic acid (TFA) provided the corresponding amine salt **14**, ready for coupling with ferulic acid **6**. On the premise that reaction of **6** with the more nucleophilic amine group of **14** is favored, the coupling was initially attempted under standard peptide coupling conditions (EDCI, $i$Pr$_2$NEt). Disappointingly, unreacted **14** was fully recovered and no trace of any coupled product could be detected. Hence, ferulic acid **6** was activated as its succinimidyl ester **15** and subjected to amide formation with **14** under basic conditions, furnishing magnolamide (**1**) in good yield (Scheme 2).

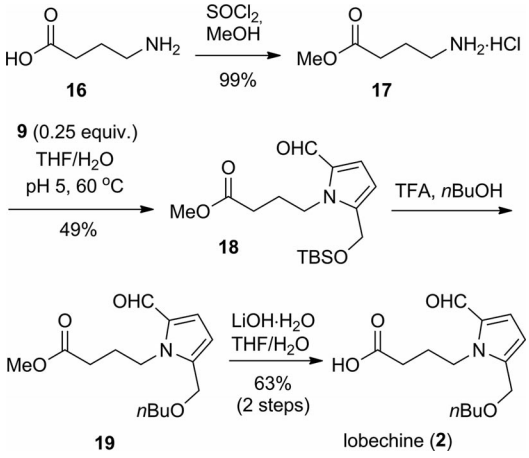
We next turned our attention to the synthesis of lobechine **2** (Scheme 3). The key amine coupling partner **17** was readily prepared from γ-aminobutyric acid **16** by standard esterification. Subsequent Maillard condensation with dihydropyranone **9** under the conditions set out in Scheme 2 resulted in some pyrrole formation, but the reaction did not proceed to completion. The recovery of the limiting reagent **9** at the end of 16 h indicated the reactive amine species **17** may be reacting with itself, hence the amount of amine was increased to 4 equiv. To our delight, dihydropyranone **9** underwent smooth Maillard coupling with amine **17**, delivering pyrrole **18** exclusively in 49% yield.

At this point, all that remained was to deprotect the TBS ether, alkylate the corresponding primary alcohol, and hydrolyze the methyl ester. During the TFA-mediated cleavage of **13**, we had detected a significant amount of methyl ether formation when methanol was used to quench the reaction. Based on this observation, we were pleased to find that on exposure to TFA in 1-butanol, TBS-protected **18**



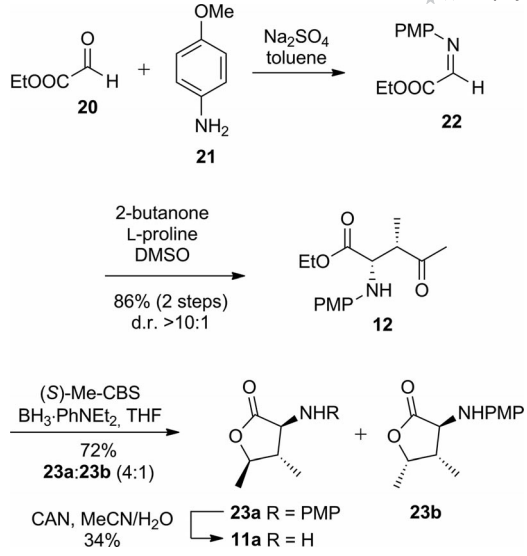

Scheme 2. Synthesis of magnolamide (**1**).




Scheme 3. Synthesis of lobechine (**2**).

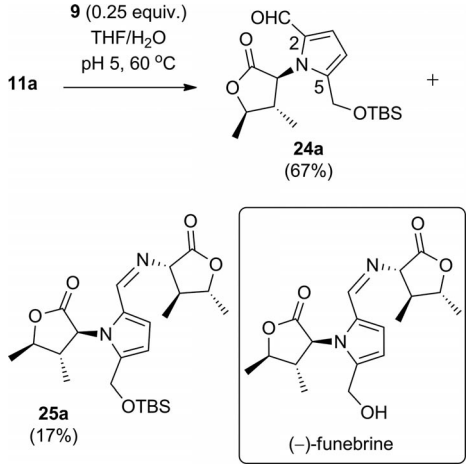
was cleanly converted into **19** in good yield. Subsequent saponification then completed the first synthesis of lobechine (**2**).

Encouraged by the newly established Maillard coupling conditions, we undertook an asymmetric total synthesis of funebral (**3**). Our initial efforts were directed towards a facile asymmetric preparation of amino lactone **11** starting from known ketone **12**[17] (Scheme 4). Following the protocol described by Barbas III,[17] imine formation between ethyl glyoxylate **20** and *p*-anisidine (**21**) followed by a proline-catalyzed Mannich reaction of intermediate **22** with 2-butanone, furnished ketone **12** in excellent yield and selectivity. CBS-mediated reduction of the ketone carbonyl subsequently provided a mixture of epimeric lactones **23a** and **23b** (*dr* 4:1) that were separable by careful column chromatography. Cleavage of the PMP protecting group of **23a** using ceric ammonium nitrate (CAN) afforded enantiopure amino lactone **11a** in 34% yield. Unfortunately, the efficiency of this reaction decreased significantly on a more practical scale (>100 mg).




Scheme 4. Synthesis of amino lactone **11**.

With a preparative amount of amino lactone **11a** secured, efforts were directed towards the critical Maillard coupling with dihydropyranone **9** (Scheme 5). Gratifyingly, a single diastereoisomer of the desired formylpyrrole adduct **24a** was obtained in moderate yield along with TBS-protected condensation product funebrine **25a**[21] and a small amount of unidentifiable decomposition products. Owing to steric crowding imposed by the substituents at the C2 and C5 positions of the pyrrole ring,[9] compound **24a** exists as a mixture of rotational isomers (determined by NMR analysis). Compound **25a** on the other hand did not exhibit rotameric NMR signals, as the concentration of the minor conformer was below the NMR detection threshold. Published NMR spectra of enantiopure (–)-funebral (**3**), for which rotameric signals were also observed, are consistent with our results.[10]

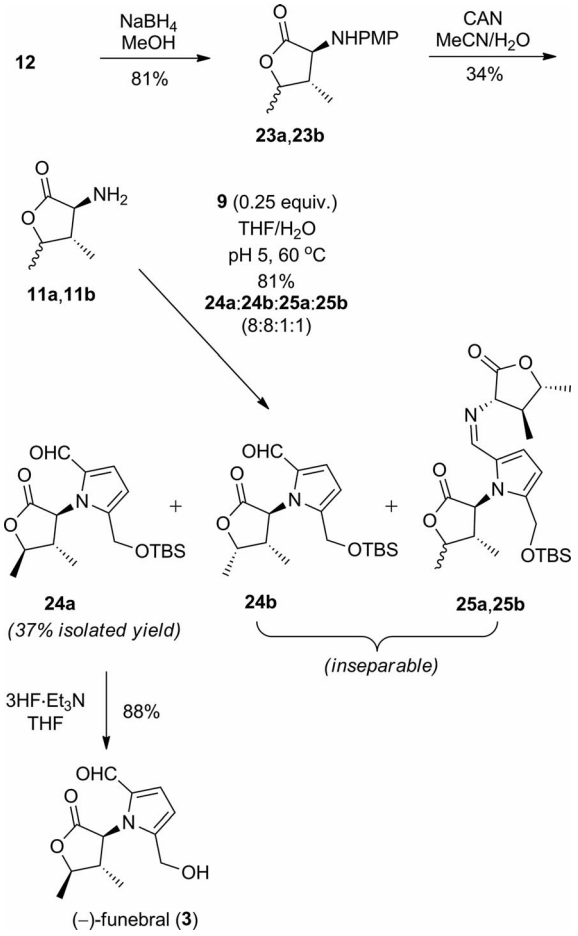



Scheme 5. Synthesis of TBS-protected funebral **24a** and TBS-protected funebrine **25a**.

In the interest of improving the efficiency and cost-effectiveness of the synthesis, we investigated the ease of preparation of enantiopure funebral (**3**) starting from an equi-

molar mixture of epimers **23a** and **23b** (Scheme 6). Accordingly, borohydride-mediated reduction of ketone **12** followed by cleavage of the PMP group provided a mixture of **11a** and **11b** in modest yield. Disappointingly, use of other oxidative cleavage methods, such as PIFA, periodic acid,[22] or trichloroisocyanuric acid,[22] did not improve the isolated yield. Further attempts to extract additional cleavage product from the aqueous phase of the reaction mixture by means of lyophilization were also unsuccessful. Moving forwards, the key Maillard condensation between the mixture of **11a** and **11b** with dihydropyranone **9** was examined under the same conditions used to obtain **24a** from **11a**. To our delight, the desired product **24a** was readily separated from epimeric **24b** and the double condensation products **25a** and **25b**, in an acceptable yield. Cleavage of the silyl ether in **24a** under pH neutral conditions completed the total synthesis of (–)-funebral (**3**). The spectroscopic data for synthetic **3** and optical rotation $\{[a]_D^{19} = -33$ ($c$ = 0.4, MeOH)} (ref. $\{[a]_D = -36.1$ ($c$ = 1.0, MeOH)}) were all in excellent agreement with those previously reported.[10]




Scheme 6. Synthesis of (–)-funebral (**3**) via an epimeric mixture of **11a** and **11b**.

## Conclusions

We have demonstrated the convenience of applying the Maillard condensation between dihydropyranone **9** and primary amines to directly access 2-formylpyrrole systems. The utility of this approach has been demonstrated through its application to the synthesis of 2-formylpyrrole natural products magnolamide (**1**), lobechine (**2**), and funebral (**3**). The spectroscopic data of synthetic **1**, **2** and **3** were all in accordance with those of the corresponding natural products. Notably, the synthesis of funebral (**3**) via an epimeric mixture of **11a** and **11b** allows for an expeditious approach to the natural product in enantiopure form, using the inexpensive catalyst L-proline as the only source of chirality. We anticipate that this chemistry will greatly facilitate the exploration of the medicinal chemistry of the biologically active 2-formylpyrrole compound family.

## Experimental Section

**General Information:** Unless otherwise stated, all nonaqueous reactions and distillations were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Dichloromethane ($CH_2Cl_2$) and toluene were freshly distilled from calcium hydride. Reactions performed at 0 °C were cooled in a water-ice bath. Flash chromatography was carried out using 0.063–0.1 mm silica gel (Davisil R LC60A 40–63 Micron) with the indicated solvent. Infrared spectra were recorded with a Perkin–Elmer R Spectrum 1000 Fourier Transform Infrared spectrometer. Values are expressed in wavenumbers ($cm^{-1}$) and recorded in a range of 4000 to 450 $cm^{-1}$. NMR spectra were recorded at 21 °C in $CDCl_3$ with either a Bruker Avance 300 spectrometer operating at 300 MHz for $^1H$ nuclei and 75 MHz for $^{13}C$ nuclei or with a Bruker DRX400 or Bruker 400 spectrometer operating at 400 MHz for $^1H$ nuclei and 100 MHz for $^{13}C$ nuclei. All chemical shifts are reported in parts per million (ppm) from tetramethylsilane ($\delta$ = 0 ppm) and were measured relative to the solvent in which the sample was analyzed ($CDCl_3$: TMS $\delta$ = 0.00 ppm for $^1H$ NMR and $CDCl_3$ $\delta$ = 77.16 ppm for $^{13}C$ NMR). Coupling constants ($J$) are reported in Hertz (Hz). $^1H$ NMR spectroscopic data is reported as chemical shift in ppm, followed by multiplicity (s singlet, d doublet, dd doublet of doublets, t triplet, m multiplet, br. broad), coupling constant where applicable and relative integral. $^{13}C$ NMR spectra are reported as chemical shift in ppm. High-resolution mass spectra were recorded with a Bruker micrOTOF-QII mass spectrometer.

**2-Formylpyrrole 13:** To a solution of *N*-Boc-1,4-butanediamine (**8**; 0.15 g, 0.8 mmol) in THF/$H_2O$ (1:1, 5 mL) was added acetic acid until the pH was brought to pH 5. Dihydropyranone **9** (0.1 g, 0.4 mmol) was added and the reaction mixture was stirred at 60 °C for 8 h. The reaction was quenched by the addition of $H_2O$ (1.5 mL) and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 9:1) afforded the title compound (95 mg, 0.2 mmol, 60%) as a yellow oil. IR (neat): $\tilde{\nu}_{max}$ = 931 (br), 1706, 1661, 1365, 1253, 1175, 838, 778 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.46 (s, 1 H), 6.84 (d, $J$ = 4.0 Hz, 1 H), 6.14 (d, $J$ = 4.0 Hz, 1 H), 4.83 (m, 1 H), 4.65 (s, 2 H), 4.31 (t, $J$ = 7.8 Hz, 2 H), 3.15 (m, 2 H), 1.79–1.72 (m, 2 H), 1.56–1.51 (m, 2 H), 1.42 (s, 9 H), 0.88 (s, 9 H), 0.06 (s, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 179.2, 155.9, 141.7, 132.1, 124.4, 109.9, 78.9, 57.2, 45.2 (2 C), 39.7, 28.3 (3 C), 27.0, 25.7 (3 C), 18.2, –5.4 (2 C) ppm. HRMS ($ESI^+$): calcd. for $C_{21}H_{39}N_2O_4Si^+$ $[M + H]^+$ 411.2674; found 411.2673.

**Hydroxysuccinimide Ferulate (15):** To a stirred solution of ferulic acid **6** (0.50 g, 2.6 mmol) in $CH_2Cl_2$ (5 mL) was added *N*-hydroxy-

succinimide (0.30 g, 2.6 mmol) and DCC (0.58 g, 2.8 mmol). The reaction mixture was stirred at room temp. for 18 h, filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 1:1) afforded the title compound as a colorless solid (0.49 g, 1.7 mmol, 66%); m.p. 153–155 °C (ref.[23] m.p. 156 °C). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ = 7.84 (d, $J$ = 16.1 Hz, 1 H), 7.27 (d, $J$ = 1.9 Hz, 1 H), 7.15 (dd, $J$ = 8.2, 2.0 Hz, 1 H), 6.83 (d, $J$ = 8.2 Hz, 1 H), 6.54 (d, $J$ = 16.1 Hz, 1 H), 3.89 (s, 3 H), 2.85 (s, 4 H) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 172.2 (2 C), 164.2, 151.8, 151.6, 149.4, 127.0, 125.4, 116.5, 112.1, 108.8, 56.5, 26.5 (2 C) ppm. The $^1$H and $^{13}$C NMR spectroscopic data closely matched those previously reported.[23]

**Magnolamide (1):** A solution of 2-formylpyrrole **13** (36 mg, 88 μmol) in $CH_2Cl_2$/TFA (1:1, 1.2 mL) was stirred at room temp. for 20 min, then the solvent was evaporated in vacuo. The resultant brown oil (**14**) was taken up in 1,4-dioxane/$H_2O$ (1:1, 2 mL), and succinimidyl ester **15** (28 mg, 96 μmol) was added followed by solid $NaHCO_3$ (7 mg, 88 μmol). The reaction mixture was stirred at room temp. for 18 h and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with aq. HCl (1 M, 3 mL) and brine (3 mL), dried with $Na_2SO_4$, and concentrated in vacuo. Purification by flash chromatography ($CH_2Cl_2$/MeOH, 19:1) afforded the title compound **1** (28 mg, 75 μmol, 86% over two steps) as a yellow oil. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ = 9.41 (s, 1 H), 7.43 (d, $J$ = 15.7 Hz, 1 H), 7.12 (d, $J$ = 1.9 Hz, 1 H), 7.02 (dd, $J$ = 8.1, 1.9 Hz, 1 H), 6.98 (d, $J$ = 4.0 Hz, 1 H), 6.79 (d, $J$ = 8.1 Hz, 1 H), 6.42 (d, $J$ = 15.7 Hz, 1 H), 6.26 (d, $J$ = 4.0 Hz, 1 H), 4.63 (s, 2 H), 4.39 (t, $J$ = 7.7 Hz, 2 H), 3.88 (s, 3 H), 3.33 (m, 2 H), 1.84–1.77 (m, 2 H), 1.64–1.57 (m, 2 H) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ = 180.9, 169.2, 149.8, 149.3, 144.5, 142.0, 133.5, 128.3, 126.4, 123.2, 118.8, 116.5, 111.6, 111.5, 56.5, 56.4, 46.3, 40.0, 29.8, 27.7 ppm. The $^1$H and $^{13}$C NMR spectroscopic data closely matched those previously reported.[1]

**2-Formylpyrrole 18:** To a solution of methyl ester **17**[24] (95 mg, 619 μmol) in THF/$H_2O$ (1:1, 3 mL) was added satd. aq. $NaHCO_3$ until the pH was brought to pH 5. Dihydropyranone **9** (40 mg, 155 μmol) was added and the reaction mixture was stirred at 60 °C for 16 h. The reaction was quenched by the addition of $H_2O$ (1 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 9:1) afforded the title compound (26 mg, 77 μmol, 49%) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 2950, 2858, 1738, 1659, 1363, 1254, 1065, 835, 776, 730 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.47 (s, 1 H), 6.85 (d, $J$ = 4.0 Hz, 1 H), 6.16 (d, $J$ = 4.0 Hz, 1 H), 4.68 (s, 2 H), 4.38 (t, $J$ = 7.5 Hz, 2 H), 3.66 (s, 3 H), 2.37 (t, $J$ = 7.5 Hz, 2 H), 2.10–2.03 (m, 2 H), 0.89 (s, 9 H), 0.07 (s, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 179.2, 173.2, 141.9, 132.2, 124.4, 110.0, 57.2, 51.6, 44.8, 31.0, 26.3, 25.8 (3 C), 18.2, –5.4 (2 C) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{29}NaNO_4Si^+$ [M + Na]$^+$ 362.1758; found 362.1759.

**Lobechine (2):** A solution of 2-formylpyrrole **18** (26 mg, 77 μmol) in *n*BuOH/TFA (1:1, 0.8 mL) was stirred at room temp. for 20 min and the solvent was evaporated under reduced pressure. The resultant purple oil (**19**) was taken up in THF/$H_2O$ (1:1, 3.8 mL) and the solution was cooled to 0 °C. LiOH·$H_2O$ (10 mg, 230 μmol) was added and the reaction mixture was stirred at room temp. for 2 h before the addition of aq. HCl (1 M) until the pH was brought to pH 2. The aqueous layer was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were washed with brine (3 mL), dried with $Na_2SO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 1:1) afforded the title compound **2** (13 mg, 48 μmol, 63%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.49 (s, 1 H), 6.88 (d, $J$ = 4.0 Hz, 1 H), 6.22 (d, $J$ = 4.0 Hz, 1 H), 4.48 (s, 2 H), 4.40 (t, $J$ = 7.5 Hz, 2 H), 3.46 (t, $J$ = 6.6 Hz, 2 H), 2.43 (t, $J$ = 7.3 Hz, 2 H), 2.11–2.03 (m, 2 H), 1.60–1.53 (m, 2 H), 1.40–1.31 (m, 2 H), 0.90 (t, $J$ = 7.3 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 179.5, 177.8, 139.3, 132.5, 124.4, 111.5, 70.4, 63.9, 44.7, 31.6, 30.8, 26.1, 19.3, 13.8 ppm. The $^1$H and $^{13}$C NMR spectroscopic data closely matched those previously reported.[2]

**Ethyl (2*S*,3*S*)-2-(*p*-Methoxyphenylamino)-3-methyl-4-oxopentanoate (12):** To a solution of *p*-anisidine **21** (2 g, 16.2 mmol) and $Na_2SO_4$ (8 g) in toluene (16 mL) was slowly added a solution of ethyl glyoxalate **20** (50% in toluene, 3.3 mL, 16.5 mmol). After 30 min, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to give imine **22**, which was taken up in DMSO (130 mL). 2-Butanone (32.5 mL) was added followed by L-proline (0.37 g, 3.2 mmol) and the reaction mixture was stirred at room temp. for 24 h. Satd. aq. $NH_4Cl$ (40 mL) was added and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 1:1) afforded the title compound **12** (3.9 g, 14.0 mmol, 86%) as a yellow oil. $[\alpha]_D^{20}$ = –80 ($c$ = 0.3, $CHCl_3$); ref.[17] $[\alpha]_D$ = –71.3 ($c$ = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.76 (d, $J$ = 8.9 Hz, 2 H), 6.64 (d, $J$ = 8.9 Hz, 2 H), 4.30 (d, $J$ = 5.9 Hz, 1 H), 4.17–4.11 (m, 2 H), 3.72 (s, 3 H), 3.04–2.97 (m, 1 H), 2.21 (s, 3 H), 1.24–1.19 (m, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 208.9, 172.6, 152.9, 140.7, 140.5, 115.6 (2 C), 114.6 (2 C), 59.5, 55.4, 49.0, 28.2, 14.0, 12.1 ppm. The $^1$H and $^{13}$C NMR spectroscopic data closely matched those previously reported.[17]

**(3*S*,4*S*,5*R*)- and (3*S*,4*S*,5*S*)-3-[(4-Methoxyphenyl)amino]-4,5-dimethyldihydrofuran-2(3*H*)-one (23a and 23b):** To a solution of (*S*)-Me-CBS catalyst (1 M in THF, 0.2 mL, 200 μmol) in THF (5 mL) was added borane *N*,*N*-diethylaniline complex (0.14 mL, 221 μmol) and the reaction mixture was stirred for 15 min before the slow, dropwise addition of ketone **12** (0.2 g, 716 μmol) in THF (4 mL). After stirring at room temp. for 1 h, the reaction mixture was diluted with MeOH/$Et_2O$ (1:40, 4 mL) then the reaction was quenched by the addition of satd. aq. $NaHCO_3$ (4 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 8 mL) and the combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 3:1) afforded compounds **23a** and **23b** (0.12 g, 516 μmol, 72%) as a mixture of diastereoisomers (*dr* 4:1). Careful flash chromatography (hexanes/EtOAc, 4:1) allowed the isolation of enantiopure **23a** as a colorless solid; m.p. 70–73 °C. $[\alpha]_D^{20}$ = –31 ($c$ = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3357, 2978, 2962, 2931, 1762, 1510, 1234, 1039, 831 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.80 (d, $J$ = 6.8 Hz, 2 H), 6.70 (d, $J$ = 6.8 Hz, 2 H), 4.14–4.08 (m, 2 H), 3.85 (d, $J$ = 11.6 Hz, 1 H), 3.76 (s, 3 H), 2.08–1.98 (m, 1 H), 1.42 (d, $J$ = 6.1 Hz, 3 H), 1.20 (d, $J$ = 6.1 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.0, 152.5, 140.6, 115.1 (2 C), 114.4 (2 C), 79.2, 61.4, 55.3, 45.5, 18.1, 13.9 ppm. HRMS (ESI$^+$): calcd. for $C_{13}H_{18}NO_3^+$ [M + H]$^+$ 236.1281; found 236.1284.

**(3*S*,4*S*)-3-[(4-Methoxyphenyl)amino]-4,5-dimethyldihydrofuran-2(3*H*)-one (23a, 23b):** To a solution of ketone **12** (0.4 g, 1.4 mmol) in MeOH (8 mL) at 0 °C was added $NaBH_4$ (60 mg, 1.6 mmol) in one portion. The reaction mixture was stirred at 0 °C for 15 min then gradually warmed to room temp. The solvent was evaporated under reduced pressure and the resultant residue was diluted with $H_2O$ (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (4 ×

10 mL) and the combined organic extracts were washed with brine (10 mL), dried with $Na_2SO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 4:1) afforded the title compounds (0.27 g, 1.2 mmol, 81%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.78 (m, 4 H), 6.69 (m, 4 H), 4.74–4.67 (m, 1 H), 4.16–4.09 (m, 1 H), 3.82 (d, $J$ = 10.4 Hz, 1 H), 3.81 (d, $J$ = 11.6 Hz, 1 H), 3.74 (s, 6 H), 2.58–2.48 (m, 1 H), 2.04–1.97 (m, 1 H), 1.43 (d, $J$ = 6.1 Hz, 3 H), 1.33 (d, $J$ = 6.8 Hz, 3 H), 1.24 (d, $J$ = 6.6 Hz, 3 H), 1.18 (d, $J$ = 6.1 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 176.2, 176.0, 152.8, 152.7, 140.7 (2 C), 115.4 (2 C), 115.3 (2 C), 114.6 (4 C), 79.4, 77.1, 61.7, 59.1, 55.4, 45.9, 40.1, 18.2, 15.5, 14.1, 12.5 ppm.

**General Procedure A: Oxidative Cleavage:** To a solution of lactone (1 equiv.) in MeCN (2 M with respect to the lactone) at 0 °C was added dropwise a solution of CAN (3 equiv.) in $H_2O$ (0.3 M with respect to the lactone). The reaction mixture was stirred at 0 °C for 1 h then washed with EtOAc. The aqueous layer was made slightly basic (pH 8) by the addition of satd. aq. $NaHCO_3$ and the inorganic solids were filtered through a sintered funnel. The filtrate was extracted with EtOAc followed by $CHCl_3$/*i*PrOH (4:1). The combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo to afford the crude product, which was purified by flash chromatography (hexanes/EtOAc, 1:4 then to $CH_2Cl_2$/MeOH, 95:5).

**(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyltetrahydro-2-furanone (11a):** Following general procedure A, reaction with lactone **23a** (0.1 g, 425 μmol) provided the title compound **11** (19 mg, 145 μmol, 34%) as a yellow oil. $[\alpha]_D^{19}$ = –18 ($c$ = 1.3, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.06–3.99 (m, 1 H), 3.24 (d, $J$ = 11.6 Hz, 1 H), 2.17 (br. s, 2 H), 1.83–1.72 (m, 1 H), 1.40 (d, $J$ = 6.1 Hz, 3 H), 1.18 (d, $J$ = 6.5 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.0, 79.7, 58.7, 47.3, 18.4, 14.0 ppm. The $^1$H NMR data closely matched those previously reported.[10]

**(3*S*,4*S*,5*R*)- and (3*S*,4*S*,5*S*)-3-Amino-4,5-dimethyltetrahydro-2-furanone (11a and 11b):** Following general procedure A, reaction of lactones **23a** and **23b** (0.1 g, 425 μmol) provided the title compounds **11a** and **11b** (19 mg, 145 μmol, 34%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.68–4.61 (m, 1 H), 4.06–3.99 (m, 1 H), 3.27 (d, $J$ = 11.4 Hz, 1 H), 3.22 (d, $J$ = 11.6 Hz, 1 H), 2.32–2.25 (m, 1 H), 1.81–1.71 (m, 1 H), 1.39 (d, $J$ = 6.3 Hz, 3 H), 1.24 (d, $J$ = 6.8 Hz, 3 H), 1.18 (d, $J$ = 6.5 Hz, 3 H), 1.14 (d, $J$ = 6.8 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.4, 178.1, 79.7, 77.2, 58.7, 55.5, 47.4, 41.7, 18.5, 15.8, 14.0, 12.6 ppm.

**General Procedure B: Maillard Condensation:** To a solution of amino lactone (4 equiv.) in THF/$H_2O$ (1:1, 0.03 M with respect to the enone) was added AcOH until the pH was brought to pH 5. Enone (1 equiv.) was added and the reaction mixture was stirred at 60 °C for 16 h. The reaction was quenched by the addition of $H_2O$, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with $Na_2SO_4$ and concentrated in vacuo to afford the crude product, which was purified by preparative thin-layer chromatography (hexanes/EtOAc, 4:1).

**TBS-Protected Funebral 24a and TBS-Protected Funebrine 25a:** Following general procedure B, reaction of amino lactone **11a** (20 mg, 155 μmol) provided the title compounds **24a** (9 mg, 26 μmol, 67%) and **25a** (3 mg, 7 μmol, 17%) as pale-yellow oils.

**Compound 24a:** $[\alpha]_D^{20}$ = +17 ($c$ = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2925, 2854, 1781, 1662, 1450, 1191, 1072, 1056, 835, 776 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.41 (s, 1 H), 7.0 (d, $J$ = 4.0 Hz, 1 H), 6.22 (d, $J$ = 4.0 Hz, 1 H), 4.99 (d, $J$ = 11.4 Hz, 1 H), 4.70 (s, 2 H), 4.26–4.19 (m, 1 H), 2.79–2.72 (m, 1 H), 1.61 (d, $J$ = 6.2 Hz, 3 H), 1.14 (d, $J$ = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.7 (2 C), 142.8, 126.0, 117.1, 110.5, 80.3, 62.7, 57.4, 43.5, 29.7, 25.8 (3 C), 18.5, 15.0, –5.1, –5.3 ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{30}NO_4Si^+$ [M + H]$^+$ 352.1939; found 352.1942.

**Compound 25a:** $[\alpha]_D^{19}$ = –25 ($c$ = 0.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2920, 2850, 1779, 1664, 1450, 1253, 1180, 1116, 1050, 835, 776 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.96 (s, 1 H), 6.59 (d, $J$ = 3.8 Hz, 1 H), 6.14 (d, $J$ = 3.9 Hz, 1 H), 5.02 (d, $J$ = 11.6 Hz, 1 H), 4.68 (d, $J$ = 3.9 Hz, 2 H), 4.17–4.11 (m, 2 H), 3.58 (d, $J$ = 10.9 Hz, 1 H), 3.23–3.16 (m, 1 H), 2.55–2.45 (m, 1 H), 1.47 (d, $J$ = 6.2 Hz, 3 H), 1.44 (d, $J$ = 6.1 Hz, 3 H), 1.10 (m, 6 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 175.0, 172.2, 155.3, 139.6, 129.9, 120.4, 109.8, 80.8, 80.5, 76.2, 62.9, 57.6, 46.2, 42.7, 29.7, 25.8 (3 C), 18.8, 18.2, 14.8, 13.8, –5.1, –5.3 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{39}N_2O_5Si^+$ [M + H]$^+$ 463.2623; found 463.2615.

**TBS-Protected Funebral (24a):** Following general procedure B, reaction of a mixture of amino lactones **11a** and **11b** (16 mg, 123 μmol) provided the title compound **24a** (4 mg, 12 μmol, 37%) along with an inseparable mixture of **24b**, **25a** and **25b** (4 mg, 41%) as pale-yellow oils.

**(–)-Funebral (3):** To a solution of silyl ether **24a** (9 mg, 26 μmol) in THF (0.2 mL) was added 3HF·$Et_3N$ (8 drops) and the reaction mixture was stirred at room temp. for 2 h. Satd. aq. $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried with $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by preparative thin-layer chromatography (hexanes/EtOAc, 1:1) afforded the title compound **3** (5.2 mg, 22 μmol, 86%) as a colorless oil. $[\alpha]_D^{19}$ = –33 ($c$ = 0.4, MeOH); ref.[10] $[\alpha]_D$ = –36.1 ($c$ = 1.0, MeOH). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.40 (s, 1 H), 7.00 (d, $J$ = 4.0 Hz, 1 H), 6.26 (d, $J$ = 4.0 Hz, 1 H), 5.05 (d, $J$ = 11.4 Hz, 1 H), 4.67 (d, $J$ = 13.7 Hz, 1 H), 4.60 (d, $J$ = 13.7 Hz, 1 H), 4.29–4.24 (m, 1 H), 2.76–2.68 (m, 1 H), 1.59 (d, $J$ = 6.2 Hz, 3 H), 1.12 (d, $J$ = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 178.9, 172.1, 142.6, 132.2, 126.1, 111.0, 80.7, 62.7, 56.6, 43.5, 18.4, 14.7 ppm. The $^1$H and $^{13}$C NMR data closely matched those previously reported.[10]

**Supporting Information** (see footnote on the first page of this article): $^1$H and $^{13}$C NMR spectra for all new compounds.

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[1] H. J. Yu, C. C. Chen, B. J. Shieh, *J. Nat. Prod.* **1998**, *61*, 1017–1019.
[2] P. C. Kuo, T. L. Hwang, Y. T. Lin, Y. C. Kuo, Y. L. Leu, *Arch. Pharmacal Res. Arch. Pharmacal Res.* **2011**, *34*, 715–722.
[3] T. M. Zennie, J. M. Cassady, R. F. Raffauf, *J. Nat. Prod.* **1986**, *49*, 695–698.
[4] J. L. Guo, Z. M. Feng, Y. J. Yang, Z. W. Zhang, P. C. Zhang, *Biol. Pharm. Bull.* **2010**, *58*, 983–985.
[5] X. G. Tong, L. L. Zhou, Y. H. Wang, C. F. Xia, Y. Wang, M. Liang, F. F. Hou, Y. X. Cheng, *Org. Lett.* **2010**, *12*, 1844–1847.
[6] W. F. Chiou, C. C. Shen, H. J. Yu, C. H. Chiang, C. C. Chen, W. Y. Chang, M. J. Don, *Heterocycles* **2005**, *65*, 1215–1220.
[7] Y. Dong, P. W. Le Quesne, *Heterocycles* **2002**, *56*, 221–226.
[8] S. X. Yu, P. W. Le Quesne, *Tetrahedron Lett.* **1995**, *36*, 6205–6208.

  

[9] Y. Dong, N. N. Pai, S. L. Ablaza, S. X. Yu, S. Bolvig, D. A. Forsyth, P. W. Le Quesne, *J. Org. Chem.* **1999**, *64*, 2657–2666.
[10] O. Tamura, N. Iyama, H. Ishibashi, *J. Org. Chem.* **2004**, *69*, 1475–1480.
[11] I. Maeba, T. Takeuchi, T. Iijima, H. Furukawa, *J. Org. Chem.* **1988**, *53*, 1401–1405.
[12] H. M. Geng, J. L. Y. Chen, D. P. Furkert, S. D. Jiang, M. A. Brimble, *Synlett* **2012**, 855–858.
[13] T. M. Woods, M. Kamalov, P. W. R. Harris, G. J. S. Cooper, M. A. Brimble, *Org. Lett.* **2012**, *14*, 5740–5743.
[14] C. Mioskowski, A. Wagner, European Patent EP1657236 A1. 17–05–2006.
[15] H. T. Cao, T. Roisnel, A. Valleix, R. Gree, *Eur. J. Org. Chem.* **2011**, 3430–3436.
[16] T. Okada, K. Sakaguchi, T. Shinada, Y. Ohfune, *Tetrahedron Lett.* **2011**, *52*, 5744–5746.
[17] A. Cordova, W. Notz, G. F. Zhong, J. M. Betancort, C. F. Barbas, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843.
[18] L. C. Maillard, *C. R. Hebd. Seances Acad. Sci.* **1912**, *54*, 66–68.
[19] L. C. Maillard, *C. R. Hebd. Seances Soc. Biol.* **1912**, *72*, 599–561.
[20] F. Ledl, E. Schleicher, *Angew. Chem.* **1990**, *102*, 597; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 565–594.
[21] R. F. Raffauf, T. M. Zennie, K. D. Onan, P. W. Le Quesne, *J. Org. Chem.* **1984**, *49*, 2714–2718.
[22] J. M. M. Verkade, L. J. C. van Hemert, P. Quaedflieg, P. L. Alsters, F. L. van Deift, F. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109–8113.
[23] W. Vanbrussel, C. F. Vansumere, *Bull. Soc. Chim. Belg.* **1978**, *87*, 791–797.
[24] F. J. Dekker, M. Ghizzoni, N. van der Meer, R. Wisastra, H. J. Haisma, *Bioorg. Med. Chem.* **2009**, *17*, 460–464.

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