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De Novo Asymmetric Synthesis of 8a-*epi*-Swainsonine

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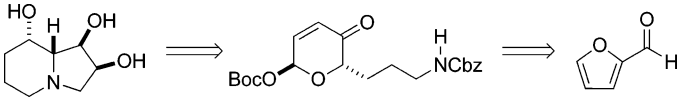

An enantioselective and diastereocontrolled approach to 8a-*epi*-D-swainsonine has been developed from achiral furfural. The key step to this synthesis was a one-pot procedure for the hydrogenolytic removal of two protecting groups and two intramolecular reductive amination reactions. The absolute stereochemistry was introduced by asymmetric Noyori reduction of furfuryl ketone. This route relies on diastereoselective palladium-catalyzed glycosylation to install the anomeric bond, and Luche reduction, diastereoselective dihydroxylation to set up the *manno*-stereochemistry of the indolizidine precursor.

Introduction

The indolizidine alkaloids widely occur in nature and have attracted great interests for the synthetic chemists because of their potent and wide range of biological activities.[1] The iminosugar natural product, (−)-swainsonine (**1**) (Figure 1), is one of the most well-known members of the polyhydroxylated indolizidine family. It was first isolated from the fungus *Rhizoctonia leguminicola*[2] and subsequently has also been found in several other plant and fungal sources.[3] Swainsonine has been shown to be a potent inhibitor of both lysosomal α-D-mannosidase[4] and mannosidase II,[5] which is also believed to be its source of anticancer, antimetastatic, antitumor-proliferative, and immunoregulating activities.[6] As part of an effort to elucidate its interesting biological properties, there has been a need for the syntheses of swainsonine,[7] its enantiomer as well as modified swainsonine derivatives. In particular, unnatural

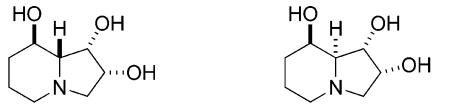

FIGURE 1. (−)-Swainsonine (**1**) and (−)-8a-*epi*-swainsonine (**2**).

diastereomers of swainsonine have become attractive synthetic targets. To date, over ten optically active diastereomers have been reported.[7a] Several of these diastereomers demonstrated comparable α-D-mannosidase inhibitory activity to (−)-swainsonine. For instance, 8a-*epi*-swainsonine (**2**) has also been shown to be an effective inhibitor of lysosomal α-D-mannosidase, with 93% the activity of swainsonine (**1**).[8]

In contrast to the synthesis of swainsonine (**1**), there have been only a few syntheses of 8a-*epi*-swainsonine (**2**).[9] As part of our program aimed at the synthesis and study of iminosugars, we became interested in the synthesis of 8a-*epi*-swainsonine (**2**), as well as its enantiomer. Previously, we reported our de novo asymmetric approach to either enantiomer of swainsonine and its epimer, 8-*epi*-swainsonine.[7m,n] The route to swainsonine occurred in only 13 steps from achiral furan and γ-butyrolactone **6** (Scheme 1).[7m] This strategy relies on a one-pot global hydrogenolysis/alkylation/reductive amination of azide sugar **3** to establish the indolizidine ring system and a regio-, diaste-

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2004**, *19*, 625−649. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1645−1680.

(2) (a) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055−2056. (b) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29−32.

(3) (a) Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926−935. (b) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257−2264. (c) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190−191.

(4) Liao, Y. F.; Lal, A.; Moremen, K. W. *J. Biol. Chem.* **1996**, *271*, 28348−28358.

(5) (a) Elbein, A. D.; Solf, R.; Dorling, P. R.; Vosbeck, K. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 7393−7397. (b) Kaushal, G. P.; Szumilo, T.; Pastuszak, I.; Elbein, A. D. *Biochemistry* **1990**, *29*, 2168−2176. (c) Pastuszak, I.; Kaushal, G. P.; Wall, K. A.; Pan, Y. T.; Sturm, A.; Elbein, A. D. *Glycobiology* **1990**, *1*, 71−82.

(6) (a) White, S. L.; Schweitzer, K.; Humphries, M. J.; Olden, K. *Biochem. Biophys. Res. Commun*. **1988**, *150*, 615−625. (b) Yagita, M.; Saksela, E. *Scand. J. Immunol*. **1990**, *31*, 275−282. (c) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot*. **1985**, *38*, 936−940.

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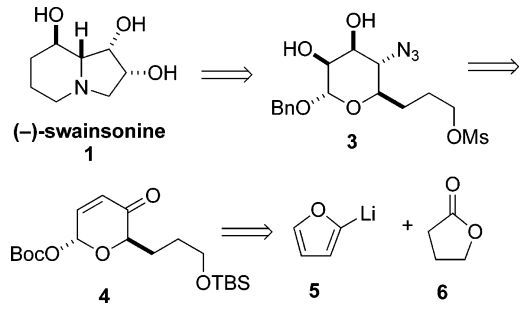
SCHEME 1. Retrosynthetic Analysis of (−)-Swainsonine (1)



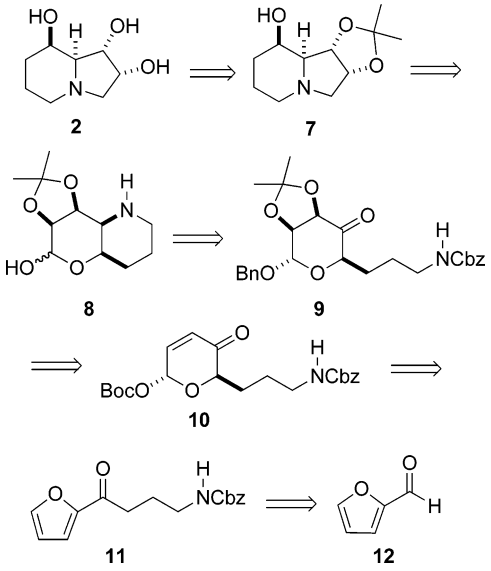
reoselective palladium-catalyzed allylation to introduce the *C*-4 azide functional group.[10] Herein we report the expansion of this de novo approach to the synthesis of 8a-*epi*-swainsonine (**2**) from achiral commercially available starting material furfural **12**. The key to the synthesis is a stereoselective one-pot reductive cyclization transformation to install the indolizidine system of 8a-*epi*-swainsonine (**2**).

Our related de novo approach to the synthesis of 8a-*epi*-swainsonine (**2**) is outlined in Scheme 2. We envisioned that the 8a-*epi*-swainsonine (**2**) could be derived from the protected 8a-*epi*-swainsonine **7**. The indolizidine ring of **7** in turn could be established from a one-pot reductive cyclization of acetonide ketone **9** via an intermediate hemiacetal **8**. The acetonide **9** would arise from diastereoselective palladium-catalyzed glycosylation, dihydroxylation, and Luche reduction of Boc-protected pyranone **10**. Finally it was envisioned that pyranone **10** could be prepared from acylfuran **11**, which in turn could be prepared from commercially available furfural (**12**).

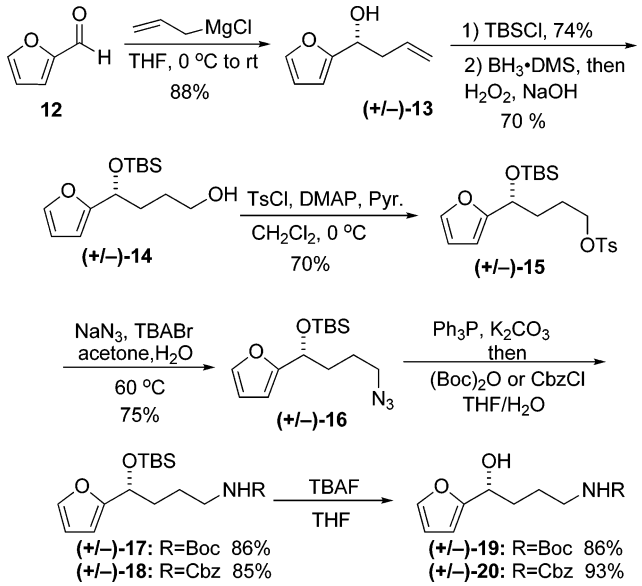
Results and Discussion

The synthesis of 8a-*epi*-swainsonine began with commercially available furfural **12** (Scheme 3), which underwent Grignard addition with allyl magnesium chloride to afford a racemic homoallylic alcohol (±)-**13** in excellent yield (88%). The

SCHEME 2. Retrosynthetic Analysis of (−)-8a-*epi*-Swainsonine (2)



SCHEME 3. Synthesis of Furfuryl Alcohols



secondary alcohol in (±)-**13** was protected as a TBS-ether (TBSCl/Et_3N) in good yield (74%), followed by a hydroboration−oxidation to give primary alcohol (±)-**14** (BH_3 then NaOOH) (70%). The primary alcohol in (±)-**14** was converted into tosylate (±)-**15** (TsCl/pyridine/DMAP), which was subsequently displaced with sodium azide to yield azide (±)-**16** in good yield for the two steps (53%). The two different *N*-protected amino furan alcohols (±)-**19** and (±)-**20** were prepared from azide (±)-**16** by a three-step approach involving azide reduction/*N*-protection/TBS-deprotection. Azide (±)-**16** was reduced with triphenylphosphine to generate a primary amine, which was protected (Boc_2O and CbzCl) in situ to provide both the Boc-amide (±)-**17** (86%) and the Cbz-amide (±)-**18** (85%). The amino furan alcohols (±)-**19** and (±)-**20** were eventually obtained after TBS-deprotection with TBAF in excellent yields ((±)-**19**: 86%; (±)-**20**: 93%). This route was amenable to the large-scale synthesis (>30 g) of the furan amino alcohols (±)-**19** and (±)-**20**.

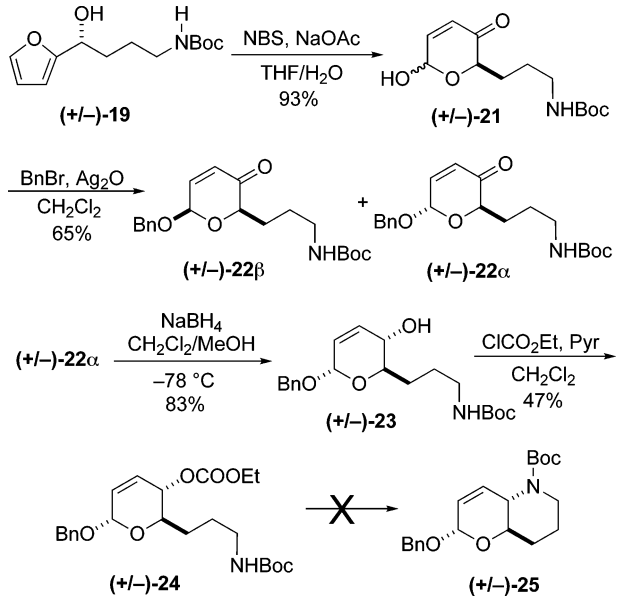
(7) For a review of swainsonine syntheses, see: (a) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579−8629. For more recent syntheses, see: (b) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325−2328. (c) Heimgaertner, G.; Raatz, D.; Reiser, O. *Tetrahedron* **2005**, *61*, 643−655. (d) Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284−7293. (e) Lindsay, K. B.; Pyne, S. G. *Aust. J. Chem.* **2004**, *57*, 669−672. (f) Pearson, W. H.; Ren, Y.; Powers, J. D. *Heterocycles* **2002**, *58*, 421−430. (g) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774−7780. (h) Buschmann, N.; Rueckert, A.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325−4329. (i) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761−1767. (j) Ceccon, J.; Greene, A. E.; Poisson, J. F. *Org. Lett.* **2006**, *8*, 4739−4712. (k) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097−7099. (l) Dechamps, I.; Pardo, D.; Cossy, J. *ARKIVOC* **2007**, *5*, 38−45. (m) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609−1612. (n) Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304−313. (o) Dechamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082−9091. For the first syntheses, see: (p) Mezher, H. A.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447−448. (q) Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853−1856.

(8) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem. J.* **1989**, *259*, 855−861.

(9) (a) Dudot, B.; Micouin, L.; Baussanne, I.; Royer, J. *Synthesis* **1999**, 688−694. (b) Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083−6089. (c) Bi, J.; Aggarwal, V. K. *Chem. Commun.* **2008**, 120−122. (d) Kim, Y. G.; Cha, J. K. *Tetrahedron Lett.* **1989**, *30*, 5721−5724. (e) Tadano, K.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3667−3671. (f) Tadano, K.; Hotta, Y.; Morita, M.; Suami, T.; Winchester, B.; Cenci di Bello, I. *Chem. Lett.* **1986**, 2105−2108.

(10) Kartika, R.; Taylor, R. E. *Chemtracts*: *Org. Chem.* **2007**, *19*, 385−390.

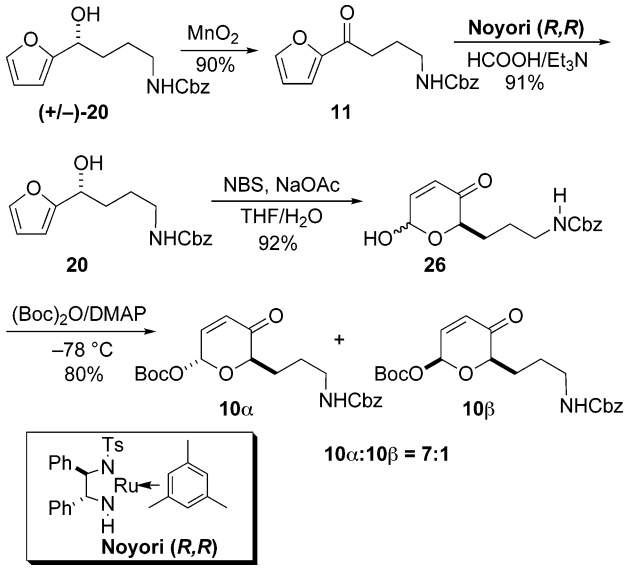
SCHEME 4. Preliminary Studies toward the Synthesis of Bicyclic *C*-4 Amino Sugar



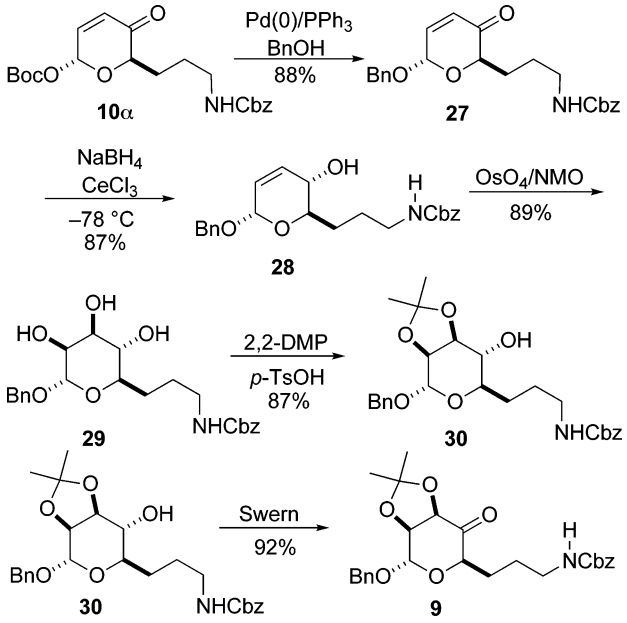
We next turned our attention to the installation of the *C*-4 amino-functionality via an intramolecular allylation strategy (Scheme 4). The racemic furfural alcohol (±)-**19** underwent oxidative ring expansion to afford the hemiacetal (±)-**21** under typical Achmatowicz conditions (NBS/NaOAc/H_2O)[11] in excellent yield (93%). The anomeric alcohol in (±)-**21** was converted to a mixture of benzyl protected pyranones (±)-**22***β* and (±)-**22**α in 1:1 ratio (BnBr/Ag_2O, 65%). The diastereomers (±)-**22***β* and (±)-**22**α were easily separated by silica gel column chromatography. Diastereoselective Luche reduction ($NaBH_4$/$CeCl_3$)[12] of α-pyranone (±)-**22**α gave allylic alcohol (±)-**23**, followed by treatment with ethyl chloroformate to form carbonate (±)-**24** in 39% yield for the two steps. Next we attempted to cyclize the carbamate of (±)-**24** to form the bicyclic adduct (±)-**25** via a palladium-catalyzed cyclization *π*-allyl intermediate. Unfortunately despite our survey of various conditions, we were unable to find any sign of the desired product (±)-**25**.[13] Similar efforts to cyclize the allylic alcohol (±)-**23** into the *C*-4 diastereomer of (±)-**25** via an S_N2 type displacement were unsuccessful. Thus, we decided to investigate alternative mechanistic approaches for the installation of the *C*-4 amino group (vide infra).

Our revised approach to 8a-*epi*-swainsonine (**2**) began with our efforts to install asymmetry into the pyranone **10**α, via an oxidation/asymmetric reduction sequence. Because of our previous success in our swainsonine (**1**) synthesis,[7m] we turned to the Noyori reduction of **11** (Scheme 5). Thus, racemic furfuryl alcohol (±)-**20** was oxidized to give furfuryl ketone **11** with MnO_2 oxidation in excellent yield (90%). Exposure of the furfuryl ketone **11** to the Noyori conditions[14] afforded an

SCHEME 5. Enantioselective Synthesis of Pyranone



SCHEME 6. Synthesis of Acetonide Ketone 9



excellent yield (91%) of furfuryl alcohol **20** in high enantiomeric excess (>96% ee).[15] Once again Achmatowicz reaction provided the ring-expanded pyranone product **26** in good yield (92%). The hemiacetal in **26** could be acylated with Boc_2O to generate the Boc-protected pyranones **10**α and **10***β* with a diastereoselectivity of 7:1 (α/*β*) and good yield (80%).[16]

With pyranone **10**α in hand, we next investigated the synthesis of acetonide **9** via a sequence of reduction/protection/oxidation reaction steps (Scheme 6). Diastereoselective palladium-catalyzed glycosylation of Boc-pyranone **10**α with

(11) (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165−176. For its recent use in carbohydrate synthesis, see: (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921−3924.

(12) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401−404.

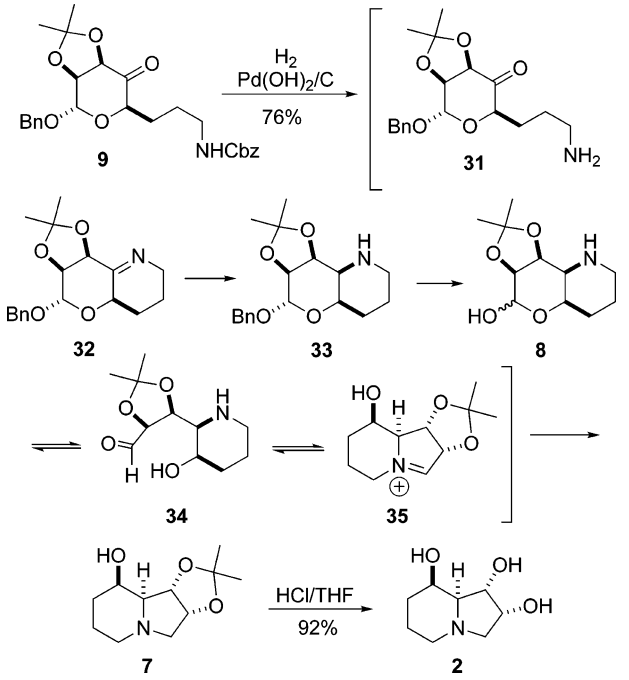
(13) Although these efforts to install the *C*-4 amino-group functionality via intramolecular cyclization were unsuccessful, the intramolecular azide displacement was very successful and led to the synthesis of swainsonine, see ref 7m.

(14) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

(15) The absolute stereochemistry and the level of enantioexcess of **20** were determined by the method of Mosher, see: (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363−1367.

(16) The relative stereochemistry and the level of diastereoselective induction were determined by analysis of the allylic coupling constants in the ^1H NMR, see: (a) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1605−1608. (b) Guppi, S. R.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 4966−4969.

SCHEME 7. Synthesis of 8a-*epi*-Swainsonine (2) via a One-Pot Reductive Cyclization Reaction



benzyl alcohol in the presence of palladium(0) and triphenylphosphine provided an *O*-benzyl ether **27** in excellent yield (88%).[17] Luche reduction of the *C*-4 ketone in **27** produced the equatorial allylic alcohol **28** in excellent yield (87%). The *manno*-stereochemistry in triol **29** was installed by dihydroxylation of allylic alcohol **28** under Upjohn conditions[18] (OsO_4/NMO) in excellent yield (89%). Selective acetonide protection of C-2/C-3 *cis*-hydroxyl groups of **29** with 2,2-dimethoxypropane and a catalytic amount *p*-TsOH afforded acetonide **30** (87%), which in turn was oxidized to provide acetonide ketone **9** under Swern conditions ($(COCl)_2$/DMSO/Et_3N, −78 °C).

To complete the synthesis of 8a-*epi*-swainsonine, a one-pot reductive cyclization was used to install the indolizidine ring (Scheme 7). This transformation involved hydrogenolytic deprotection and double reductive amination with a catalytic amount of palladium hydroxide and 1 atm of hydrogen gas. Hydrogenolysis of the Cbz-protecting group in **9** should provide primary amine **31**, which could be converted into Schiff base **32**. Amino sugar **33** would be formed by hydrogenation of imine **32**. Hydrogenolytic deprotection of the Bn-protecting group in **33** should give hemiacetal **8**, which can equilibrate to intermediate hydroxy aldehyde **34**. An intramolecular reductive amination of **34** should afford the protected 8a-*epi*-swainsonine **7** via a bicyclic iminium ion intermediate **35**. Finally, 8a-*epi*-swainsonine (**2**) was obtained by acidic hydrolysis of the acetonide **7** in excellent yield (70%, two steps) after ion-exchange chromatography (Basic HO^- form).

Conclusions

In conclusion, a de novo asymmetric approach to 8a-*epi*-swainsonine (**2**) has been developed. This highly enantio- and diastereocontrolled route illustrates the utilities of Noyori reduction, palladium-catalyzed glycosylation, diastereoselective dihydroxylation, and one-pot reductive cyclization. This 8a-*epi*-swainsonine was achieved in 19 steps and 5.1% overall yield from achiral furfural **12**. Further application of this approach to the synthesis of various analogues and biological activity testing is ongoing.

Experimental Section[19]

Benzyl 4-(Furan-2-yl)-4-oxobutylcarbamate (11). To a solution of alcohol (±)-**20** (2.89 g, 10 mmol) in THF (50 mL) was added activated MnO_2 (13 g) then the solution was left to stir for 12 h and the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure to yield furfuryl ketone **11** (2.58 g, 9.0 mol, 90%): colorless oil, R_f 0.48 (60% EtOAc/hexane); IR (thin film, cm^{-1}) 3343, 2943, 1672, 1529, 1468, 1250, 1018, 758; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 1.8 Hz, 1H), 7.29−7.35 (m, 5H), 7.17 (d, J = 3.6 Hz, 1H), 6.52 (dd, J = 3.6, 1.8 Hz, 1H), 5.08 (s, 2H), 4.94 (br, 1H), 3.74 (q, J = 6.6 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 1.94 (p, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.9, 156.5, 152.7, 146.4, 136.7, 128.6, 128.2 (2 C), 117.2, 112.3, 66.7, 40.7, 35.6, 24.3; ClHRMS calcd for [$C_{16}H_{17}NO_4H^+$] 288.1236, found 288.1235.

Benzyl (R)-4-(Furan-2-yl)-4-hydroxybutylcarbamate (20). To a 5 mL flask was added furfuryl ketone **11** (5.74 g, 20 mmol), CH_2Cl_2 (20 mL), formic acid/triethylamine 26 mL (5:7, molar ratio), and Noyori asymmetric transfer hydrogenation catalyst (*S*)-Ru(η^6-mesitylene)-(*R*,*R*)-TsDPEN (241 mg, 2.0 mol %). The resulting solution was stirred at room temperature for 24 h. Water (80 mL) was added to dilute and the reaction was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude oil. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexane to give furyl alcohol **20** (28.7 g, 106.4 mmol, 91%): white solid; R_f 0.35 (60% EtOAc/hexane); mp 143−144 °C; $[\alpha]^{25}_D$ +11 (*c* 1.2, CH_2Cl_2); IR (thin film, cm^{-1}) 3417, 3338, 2943, 1699, 1529, 1258, 1010, 739; ^1H NMR (600 MHz $CDCl_3$) δ 7.29−7.36 (m, 6H), 6.32 (dd, J = 3.6, 1.8 Hz, 1H), 6.22 (d, J = 1.8 Hz, 1H), 5.08 (s, 2H), 4.88 (br, 1H), 4.70 (q, J = 6.6 Hz, 1H), 3.23 (m, 2H), 2.26 (d, J = 4.8 Hz, 1H, OH), 1.87 (m, 2H), 1.66 (s, J = 6.6 Hz, 1H), 1.57 (s, J = 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (2 C), 142.0, 136.7, 128.6 (2 C), 128.2, 110.2, 106.0, 67.5, 66.7, 40.8, 32.6, 26.2; ClHRMS calcd for [$C_{16}H_{19}NO_4Na^+$] 312.1212, found 312.1211.

***tert*-Butylcarbonate 3-((2*R*,6*S*)-6-(Benzyloxy)-3,6-dihydro-3-oxo-2*H*-pyran-2-yl)propylcarbamate (10α).** Furyl alcohol **20** (2.0 g, 6.92 mmol), 21 mL of THF, and 7 mL of H_2O were added to a round-bottom flask then the mixture was cooled to 0 °C. Solid $NaHCO_3$ (1.16 g, 13.8 mmol), $NaOAc{\cdot}3H_2O$ (1.41 g, 10.3 mmol), and NBS (1.2 g, 6.92 mmol) were added to the solution and the mixture was stirred for 0.5 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ (50 mL), extracted (3 × 50 mL) with Et_2O, dried (Na_2SO_4), concentrated under reduced pressure, and purified by silica gel chromatography eluting with 60% EtOAc/hexane to give hemiacetal **26** (1.94 g, 6.37 mmol, 92%): R_f 0.35 (60% EtOAc/hexane). Hemiacetal **26** (1.94 g, 6.37 mmol) was dissolved in CH_2Cl_2 (4.4 mL) and the solution was cooled to −78 °C. A CH_2Cl_2 (2.0 mL) solution of $(Boc)_2O$ (1.65 g, 7.6 mmol) and a catalytic amount of DMAP (150 mg, 1.23 μmol) were added to the reaction

(17) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc*. **2003**, *125*, 12406−12407. For its application in the de novo syntheses see: (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc*. **2004**, *126*, 3428−3429. (c) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206−5208.

(18) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973−1976. (b) Shan, M.; O'Doherty, G. A. *Org. Lett*. **2006**, *8*, 5149−5152.

(19) Presented in this Experimental Section are the experimental procedures and spectral data for the new compounds required for the synthesis of 8a-*epi*-swainsonine. Complete experimental procedures and spectral data for all compounds are presented in the Supporting Information.

mixture. The reaction was stirred for 14 h at −78 °C and quenched with 100 mL of saturated $NaHCO_3$, extracted with Et_2O (3 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified with silica gel flash chromatography eluting with 10% EtOAc/hexane to give 2.06 g (5.1 mmol, 80%) of two diastereomers of Boc-protected pyranone **10**α and **10**β in 7:1: R_f 0.21 (30% Et_2O/hexane); $[\alpha]^{25}_D$ −46 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3347, 2979, 2932, 1749, 1698, 1525, 1274, 1252, 1154, 941, 843; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28−7.35 (m, 5H), 6.86 (dd, J = 10.2, 3.6 Hz, 1H), 6.32 (d, J = 3.6 Hz, 1H), 6.20 (d, J = 10.2 Hz, 1H), 5.08 (s, 2H), 4.84 (m, 1H), 4.52 (dd, J = 7.2, 3.6 Hz, 1H), 3.62 (m, 2H), 1.97−2.03 (m, 1H), 1.73−1.80 (m, 1H), 157−1.68 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 195.1, 156.4, 151.9, 141.1, 136.7, 128.8, 128.6, 128.2, 128.1, 89.2, 83.8, 75.3, 66.7, 40.6, 27.7, 26.6, 25.2; ClHRMS calcd for [$C_{21}H_{27}NO_7H^+$] 406.1866, found 406.1862.

Benzyl 3-((2*R*,6*S*)-6-(Benzyloxy)-3,6-dihydro-3-oxo-2*H*-pyran-2-yl)propylcarbamate (27). To a solution of Boc-protected pyranone **10**α (773 mg, 1.91 mmol) and benzyl alcohol (0.41 g, 3.82 mmol) in dry CH_2Cl_2 (1.9 mL) was added a CH_2Cl_2 (1.9 mL) solution of $Pd_2(DBA)_3$·$CHCl_3$ (24.6 mg, 2.5 mol % Pd) and PPh_3 (25.5 mg, 10 mol %) at 0 °C under an argon atmosphere. After being stirred for 2 h from 0 °C to room temperature, the reaction mixture was quenched with 50 mL of saturated $NaHCO_3$, extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified with silica gel flash chromatography eluting with 10% EtOAc/hexane to give benzyl ether **27** (664 g, 1.68 mmol, 88%) as a colorless oil: R_f 0.21 (30% EtOAc/hexane); $[\alpha]^{25}_D$ −24 (*c* 1.1, CH_2Cl_2); IR (thin film, cm^{-1}) 3357, 3033, 2937, 1695, 1525, 1246, 1097, 1024, 737; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29−7.38 (m, 10H), 6.83 (dd, J = 10.2, 3.0 Hz, 1H), 6.10 (d, J = 10.2 Hz, 1H), 5.28 (d, J = 3.0 Hz, 1H), 5.10 (s, 2H), 4.90 (br, 1H), 4.81 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.44 (dd, J = 7.2, 3.6 Hz, 1H), 3.23 (m, 2H), 1.94−1.99 (m, 1H), 1.68−1.75 (m, 1H), 1.55−1.67 (m, 2H); ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 196.3, 156.4, 143.5, 137.1, 136.7, 128.6 (2 C), 128.5, 128.2, 128.1 (2 C), 127.8, 92.3, 73.8, 70.9, 66.6, 40.9, 26.7, 25.6; CIHRMS calcd for [$C_{23}H_{25}O_5NNa^+$] 418.1630, found 418.1631.

Benzyl 3-((2*R*,3*R*,6*S*)-6-(Benzyloxy)-3,6-dihydro-3-hydroxy-2*H*-pyran-2-yl)propylcarbamate (28). A CH_2Cl_2 (0.57 mL) solution of pyranone **27** (450 mg, 1.14 mmol) and MeOH/$CeCl_3$ (0.57 mL, 1 M) was cooled to −78 °C. $NaBH_4$ (45 mg, 1.17 mmol) was added and the reaction mixture was stirred at − 78 °C for 0.5 h. The reaction mixture was diluted with ether (20 mL) and quenched with 25 mL of saturated $NaHCO_3$, extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (60% EtOAc/hexane) to give 393 mg (0.99 mmol, 87%) of allylic alcohol **28** as a colorless oil: R_f 0.18 (50% EtOAc/hexane); $[\alpha]^{25}_D$ +24 (*c* 0.9, CH_2Cl_2); IR (thin film, cm^{-1}) 3346, 2937, 2878, 1698, 1530, 1254, 1021, 734; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24−7.37 (m, 10H), 5.95 (dd, J = 10.2, 1.2 Hz, 1H), 5.77 (ddd, J = 10.2, 2.7, 2.3 Hz, 1H), 5.09 (s, 2H), 5.03 (d, J = 1.2 Hz, 1H), 4.93(br, 1H), 4.79 (d, J = 11.6 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 3.88 (dd, J = 8.1, 7.4 Hz, 1H), 3.65 (dd, J = 9.2, 7.2 Hz, 1H), 3.26 (m, 2H), 2.15 (d, J = 7.6, 1H, OH), 1.85−2.01 (m, 1H), 1.71−1.83 (m, 1H), 1.41−1.63 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.7, 137.8, 136.6, 133.8, 128.6 (2 C), 128.5, 128.2, 128.0, 127.8, 126.5, 93.5, 71.5, 71.2, 67.9, 66.7, 40.9, 28.9, 26.1; CIHRMS calcd for [$C_{23}H_{27}O_5NNa^+$] 420.1787, found 420.1790.

Benzyl 3-((2*R*,3*S*,4*S*,5*S*,6*S*)-6-(Benzyloxy)tetrahydro-3,4,5-trihydroxy-2*H*-pyran-2-yl)propylcarbamate (29). To a *tert*-butyl alcohol/acetone (1.52 mL, 1:1, 1 M) solution of allylic alcohol **28** (300 mg, 0.76 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methylmorpholine *N*-oxide/water (0.76 mL). Crystalline OsO_4 (2.0 mg, 1 mol %) was added. The reaction mixture was stirred for 24 h, concentrated onto a small amount of silica gel under reduced pressure, then purified by silica gel flash chromatography (4% MeOH/Et_2O) to give triol **29** (199 mg, 0.48 mmol, 89%); R_f 0.06 (60% EtOAc/hexane); mp 48−52 °C; $[\alpha]^{25}_D$ −56 (*c* 1.0, MeOH); IR (thin film, cm^{-1}) 3387, 2927, 1691, 1455, 1429, 1361, 1061; ^{1}H NMR (600 MHz, CD_3OD) δ 7.33−7.42 (m, 10H), 5.14 (s, 2H), 4.86 (s, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 3.91 (dd, J = 3.6, 1.8 Hz, 1H), 3.78 (dd, J = 9.0, 3.6 Hz, 1H), 3.59 (m, 1H), 3.54 (dd, J = 9.0, 9.0 Hz, 1H), 3.24 (t, J = 7.2 Hz, 2H), 1.96−2.01 (m, 1H), 1.82−1.89 (m, 1H), 1.62−1.69 (m, 1H), 1.54−1.62 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 159.0, 139.1, 138.6, 129.6, 129.2, 129.0, 128.9 (2 C), 128.8, 100.7, 73.6, 72.8, 72.5, 72.3, 70.1, 67.4, 42.1, 29.9, 27.4; CIHRMS calcd for [$C_{23}H_{29}O_7NNa^+$] 454.1842, found 454.1841.

Benzyl 3-((3a*S*,4*S*,6*R*,7*R*,7a*S*)-4-(Benzyloxy)tetrahydro-7-hydroxy-2,2-dimethyl-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)propylcarbamate (30). *p*-Toluenesulfonic acid monohydrate (43.3 mg, 5 mol %) was added to a stirred solution of triol **29** (2.0 g, 4.64 mmol) and 2,2-dimethoxypropane (13.0 mL) in acetone (46 mL) for 0.5 h at 0 °C. The reaction mixture was quenched with sodium bicarbonate solution (20 mL), acetone was removed in vacuo, then the reaction mixture was extracted with Et_2O (3 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified with silica gel flash chromatography eluting with 50% EtOAc/hexane to give 1.90 g (4.04 mmol, 87%) of acetonide **30** as a colorless oil: R_f 0.59 (60% EtOAc/hexane); mp 118−120 °C; $[\alpha]^{25}_D$ +32 (*c* 0.8, CH_2Cl_2); IR (thin film, cm^{-1}) 3355, 2985, 2934, 1698, 1525, 1455, 1243, 1219, 1066, 1023, 911; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.38 (m, 10H), 5.13(br, 1H, NH), 5.10 (s, 2H), 5.07 (s, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.18 (d, J = 6.0 Hz, 1H), 4.11 (dd, J = 6.0, 7.2 Hz, 1H), 3.61 (ddd, J = 9.0, 9.0 Hz, 1H), 3.44 (m, 2H), 3.23 (m, 2H), 1.74−1.99 (m, 2H), 1.39−1.66 (m, 2H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.5, 136.8, 136.5, 128.5, 128.4, 128.1 (2 C), 128.0, 127.9, 109.3, 96.0, 78.6, 75.7, 72.8, 69.3, 69.0, 66.6, 40.9, 28.3, 28.0, 26.2, 25.9; CIHRMS calcd for [$C_{26}H_{33}NO_7Na^+$] 494.2149, found 494.2154.

Benzyl 3-((3a*S*,4*S*,6*R*,7a*R*)-4-(Benzyloxy)tetrahydro-2,2-dimethyl-7-oxo-3a*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)propylcarbamate (9). To a solution of $(COCl)_2$ (0.17 mL, 2 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.58 mL, 4.0 mmol) at −78 °C, and the mixture was stirred for 10 min. A solution of alcohol **30** (471 mg, 1 mmol) in 2 mL of CH_2Cl_2 was added to the resulting mixture, with stirring for 0.5 h at −78 °C. Then triethylamine (0.57 mL, 4.0 mmol) was added at −78 °C and the reaction mixture was warmed to 0 °C for 1 h. Water (50 mL) was added to quench the mixture, and the aqueous mixture was extracted with Et_2O (3 × 80 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified with silica gel flash chromatography eluting with 50% Et_2O/hexane to give ketone **9** (431 mg, 1.84 mmol, 92%) as a colorless oil: R_f 0.53 (40% EtOAc/hexane); $[\alpha]^{25}_D$ +83 (*c* 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 3376, 2934, 1709, 1521, 1455, 1229, 1073, 1018, 910, 857; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27−7.39 (m, 10H), 5.09 (s, 2H), 5.04 (s, 1H), 5.0 (br, 1H), 4.72 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.47 (dd, J = 6.6, 1H), 4.43 (d, J = 6.6, 1H), 4.18 (dd, J = 4.8, 8.4 Hz, 1H), 3.2 (m, 2H), 1.22−1.92 (m, 4H), 1.46 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 204.0, 156.4, 136.6, 136.3, 128.6, 128.5, 128.2, 128.1, 128.0 (2 C), 111.4, 95.9, 78.6, 75.8, 73.4, 70.0, 66.6, 40.7, 27.6, 26.7, 25.9, 25.4; CIHRMS calcd for [$C_{26}H_{31}O_7NNa^+$] 492.1998, found 492.1999.

(3a*R*,9*R*,9a*S*,9b*S*)-Octahydro-2,2-dimethyl-[1,3]dioxolo[4,5-*a*]-indolizin-9-ol (7). To a solution of acetonide ketone **9** (300 mg, 0.68 mmol) in dry EtOH/THF (3 mL, v/v = 1:1) was added Pd-$(OH)_2$/C (100 mg). The reaction mixture was stirred under an atmosphere of H_2 at room temperature for 3 days, filtered off through a short pad of Celite, and concentrated under reduced pressure. The resulting crude product was purified with silica gel flash chromatography eluting with 10% MeOH/EtOAc to give protected (−)-8a-*epi*-D-swainsonine **7** (111 mg, 0.52 mmol, 76%); R_f 0.68 (50% MeOH/EtOAc); $[\alpha]^{25}_D$ −25 (*c* 1.35, CH_2Cl_2); IR (neat,

cm^{-1}) 3396, 2985, 2935, 2803, 1373, 1207, 1159, 1071, 866; ^1H NMR (600 MHz, $CDCl_3$) δ 4.66 (dd, J = 6.6, 6.0 Hz, 1H), 4.56 (q, J = 6.0 Hz, 1H), 4.05 (m, 1H), 3.39 (dd, J = 9.0, 6.0 Hz, 1H), 2.96 (dt, J = 10.8, 3.0 Hz, 1H), 2.49 (br. s, 1H), 2.37 (m, 1H), 2.24 (m, 2H), 1.90 (m, 1H), 1.77 (m, 1H), 1.38−1.53 (m, 2H), 1.51 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 113.9, 79.9, 77.3, 72.4, 64.7, 60.4, 52.4, 30.8, 27.2, 25.1, 19.1; CIHRMS calcd for [$C_{11}H_{19}NO_3H^+$] 214.1443, found 214.1438.

(1*S*,2*R*,8*R*,8a*S*)-Octahydroindolizine-1,2,8-triol (2).[9c] To a solution of protected (−)-8a-*epi*-D-swainsonine **7** (40 mg, 0.14 mmol) in THF (0.4 mL) was added 6 N HCl (0.20 mL) at room temperature and the reaction was stirred over night. The resulting mixture was concentrated under reduced pressure and then eluted with water through an ion exchange column (Dowex 1 × 8 200 OH^-, 200 mg). Removal of water in vacuo gave a white powder, (−)-8a-*epi*-D-swainsonine **2** (30 mg, 0.13 mmol, 92%): R_f 0.22 (50% MeOH/EtOAc); mp 117−119 °C [lit.[9c] mp 116−118 °C]; $[\alpha]^{25}_D$ −63 (*c* 1.0, MeOH) [lit.[9c] $[\alpha]^{21}_D$ −64 (*c* 0.95, MeOH)]; IR (thin film, cm^{-1}) 3350, 2934, 2801, 1644, 1329, 1157, 1057, 1003; ^1H NMR (600 MHz, D_2O, ref CD_3OD) δ 4.32 (q, J = 6.6 Hz, 1H), 4.10 (m, 1H), 3.91 (dd, J = 9.0, 6.6 Hz, 1H), 3.39 (dd, J = 10.2, 6.6 Hz, 1H), 2.95 (dd, J = 10.2, 1.8 Hz, 1H), 2.14 (dd, J = 10.2, 6.6 Hz, 1H), 2.10 (m, 2H), 1.87−1.90 (m, 1H), 1.69−1.77 (m, 1H), 1.50−1.58 (m, 2H); ^{13}C NMR (150 MHz, D_2O, ref CD_3OD) δ 70.7, 70.5, 67.7, 64.4, 61.4, 53.4, 30.9, 20.1 [lit.[9c] (D_2O, ref CH_3OH, 100 MHz) δ 60.65, 69.41, 66.69, 63.39, 60.37, 52.33, 29.85, 19.10]; CIHRMS calcd for [$C_8H_{15}NO_3H^+$] 174.1130, found 174.1125.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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