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Asymmetric Synthesis of 2,4,5-Trisubstituted Piperidines from Sulfinimine-Derived δ-Amino β-Ketoesters. Formal Synthesis of Pseudodistomin B Triacetate

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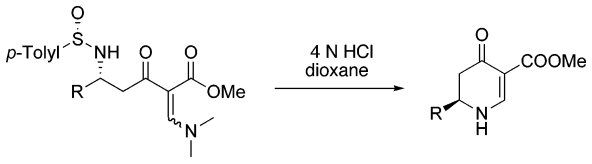
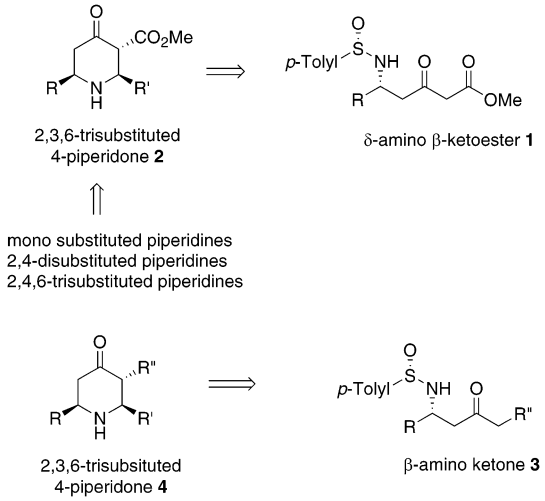


N-Sulfinyl δ-amino β-ketoester enaminones, a new sulfinimine-derived chiral building block, undergoes, on hydrolysis in one pot, an intramolecular Michael addition followed by a retro-Michael-type elimination to give enantiopure 2,4,5-trisubstituted piperidines, a structural motif found in numerous biologically active alkaloids. This new chiral building block is readily prepared by treating *N*-sulfinyl δ-amino β-ketoesters with dimethylformamide dimethyl acetal. This new protocol was illustrated with a concise formal asymmetric synthesis of marine alkaloid pseudodistomin B triacetate.

Piperidines are among the most common structure features of many alkaloid natural products, bioactive compounds, drugs, and drug candidates. As a consequence, numerous methods have been devised for their synthesis, and they are the subject of several recent reviews.[1] Currently, the challenge is to develop asymmetric syntheses of multisubstituted piperidines that are not only concise but also have the necessary substitution patterns and functionalities for the synthesis of more elaborate derivatives. Recent efforts in our laboratory have exploited the intramolecular Mannich[2] reaction of the free amine derived from *N*-sulfinyl δ-amino β-ketoesters **1** and diverse aldehydes (R′CHO) for the highly diastereoselective asymmetric synthesis of 2,3,4,6 tetrasubstituted 4-piperidones **2** (Scheme 1).[3] This chiral building block was employed in concise asymmetric syntheses of monosubstituted piperidines such as (*R*)-(+)-2-phenylpiperidine;[4] disubstituted piperidines such as the four isomers of 4-hydroxypipecolic acid[5] and (−)-SS20846A;[4] and trisubstituted piperidines including the frog skin toxin (+)-241D[6] and the quinolizidine alkaloids (−)-lasubine I,[7] (+)-lasubine II,[8] and (−)-epimyrtine.[9] In

SCHEME 1



(1) For reviews on the asymmetric synthesis of piperidines, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693. (c) Weintraub, P. M.; Sabol, J. S..; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

(2) For a review of the application of the Mannich reaction in alkaloid synthesis, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed*. **1998**, *37*, 1044.

(3) For a review, see: Zhou, P.; Chen, B.-C.; Davis, F. *Tetrahedron* **2004**, *60*, 8030.

(4) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041.

(5) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.

(6) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett*. **2001**, *3*, 3169.

(7) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623.

(8) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855.

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TABLE 1. Reaction of 5 with TFA and Dimethoxymethane

						isolated yield (%)		
entry	$CH_2(OMe)_2$ (equiv)	TFA (equiv)	solvent	scale (mmol)	*T* (°C)	**7**	(+)-**8**	(−)-**9**
1	2	6	PhMe	0.15	80	10−30		
2	2	3	PhMe	0.15	80		40	5
3	2	6	PhMe	0.15	80		15	50
4	20	6	PhMe	0.15	80		40	10
5	2	6	PhMe	0.15	60		20	20
6	2	6	DCM	0.15	40		10	0
7	2	6	PhMe	0.3	80		15	30
8	2	6	PhMe	0.3	80		15[a]	30
9	0	6	DCM	0.15	40		70	0

[a] Reaction run in a sealed tube.

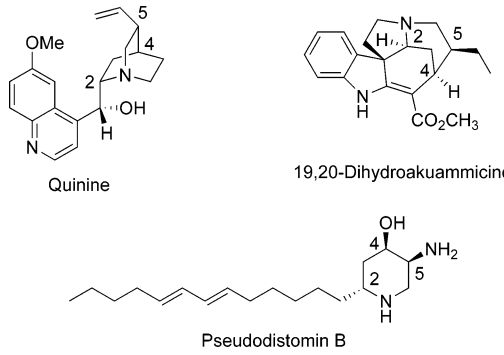


FIGURE 1. Examples of 2,4,5-trisubstituted piperidines.

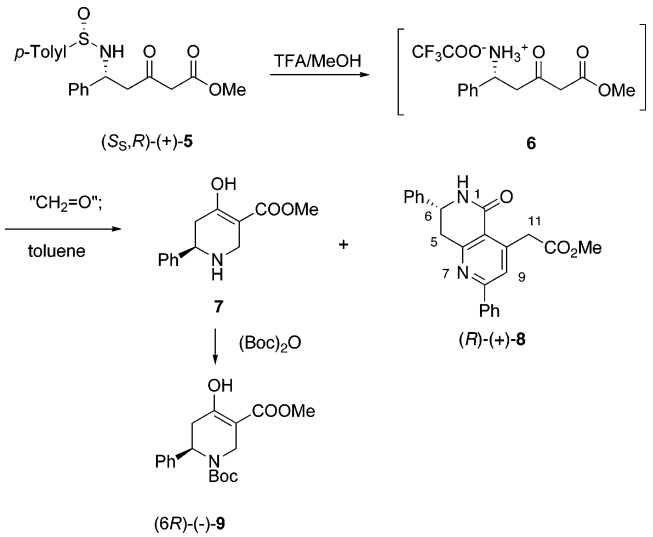
a similar fashion, the intramolecular Mannich reaction of aldehydes (R′CHO) with enantiopure *β*-amino ketones **3** afforded 2,4,6-trisubstituted[10] and 2,3,4,6-tetrasubstituted 4-piperidones **4** (Scheme 1).[11] An example of this latter type of piperidone, one which has a methyl group in the 3-position, was concisely elaborated into indolizidine 209B, a 2,3,6-trisubstitued piperidine moiety.[11]

Numerous piperidine alkaloid natural products have the 2,4,5-trisubstituted pattern and a few examples are given in Figure 1. To access these types of piperidines using the Mannich protocol and *N*-sulfinyl *δ*-amino *β*-ketoesters **1** requires reaction with formaldehye (CH_2O) or its equivalent. Described herein are studies aimed at this objective that result in a formal asymmetric synthesis of pseudodistomin B triacetate.

Result and Discussion

(S_S,*R*)-(+)-Methyl 3-oxo-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (**5**) was prepared, as previously described, and treated with 5 equiv of TFA in MeOH to remove the *N*-sulfinyl auxiliary (Scheme 2).[5] This provides the free amine as the triflate salt **6** (Scheme 2). We previously reported that a short column was necessary to remove the sulfinyl byproducts prior to reaction with the aldehyde and the Mannich cyclization.[4−7] However, we discovered that the intramolecular Mannich reaction works without purification of **6**, and the presence of the sulfinyl byproducts has no influence on the reaction outcome.[12] Therefore, to affect the Mannich cyclization **5** was treated with TFA, formaldehyde, and various formaldehyde precursors with the goal of preparing 2,4,5-trisubstituted piperidone **7** (Scheme 2).

SCHEME 2



All attempts to affect the Mannich cyclization using formaldehyde gas, generated by heating paraformaldehyde, or aqueous formaldehyde resulted in complex mixtures of products in which **7** was not detected. Dimethoxymethane, which has been reported to be a useful source of formaldehyde, proved to be successful.[13] Thus, heating **5** with dimethoxymethane and TFA in toluene resulted in a crude yield of enol **7**, in 10−30% yield (Table 1, entry 1). However, this material proved to be difficult to isolate and purify. Therefore, following chromatography **7** was immediately converted into *N*-Boc derivative (−)-**9** by treatment with $(Boc)_2O/Et_3N$. Another product, bicyclic pyridine (+)-**8**, was also isolated (Scheme 2). It soon became apparent that the yields of these products were very sensitive to the solvent, the concentration, and the reaction temperature. These results are summarized in Table 1.

With less than 6 equiv of TFA or temperatures lower than 80 °C the yield of (−)-**7**/**9** was reduced (Table 1,

(9) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem*. **2003**, *68*, 8061.

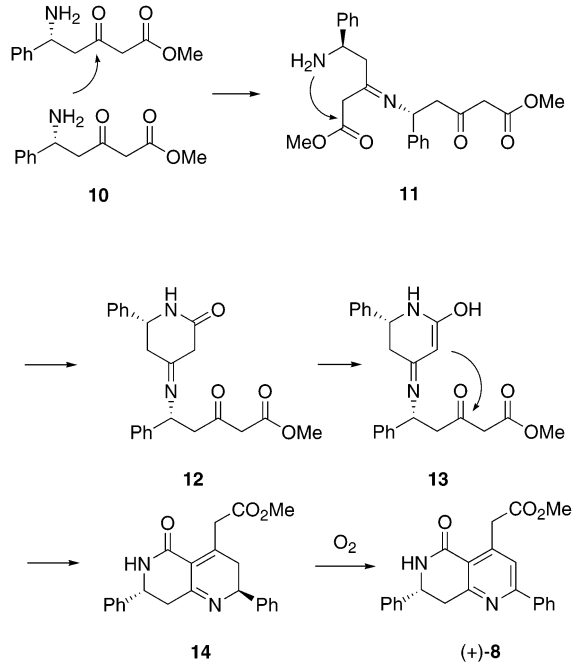
(10) (a) Ripoche, I.; Canet, J.; Gelas, J.; Troin, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 2213. (b) Ciblat, S.; Besse, P.; Canet, J.; Troin, Y.; Veschambre, H.; Gelas J. *Tetrahedron: Asymmetry* **1999**, *10*, 2225. (c) Besse, P.; Ciblat, S.; Canet, J.; Troin, Y.; Veschambre H. *Tetrahederon: Asymmetry* **2000**, *11*, 2211. (d) Glasson, S. R.; Canet, J.-L.; Troin, Y. *Tetrahedron Lett*. **2000**, *41*, 9797. (e) Ciblat, S.; Calinaud, P.; Canet, J.-L.; Troin, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 353. (f) Carbonnel, S.; Troin, Y. *Heterocycles* **2002**, *57*, 1807. (g) Lamazzi, C.; Carbonnel, S.; Calinaud, P.; Troin Y. *Heterocycles* **2003**, *60*, 1447.

(11) Davis, F. A.; Yang, B. *Org. Lett*. **2003**, *5*, 5011.

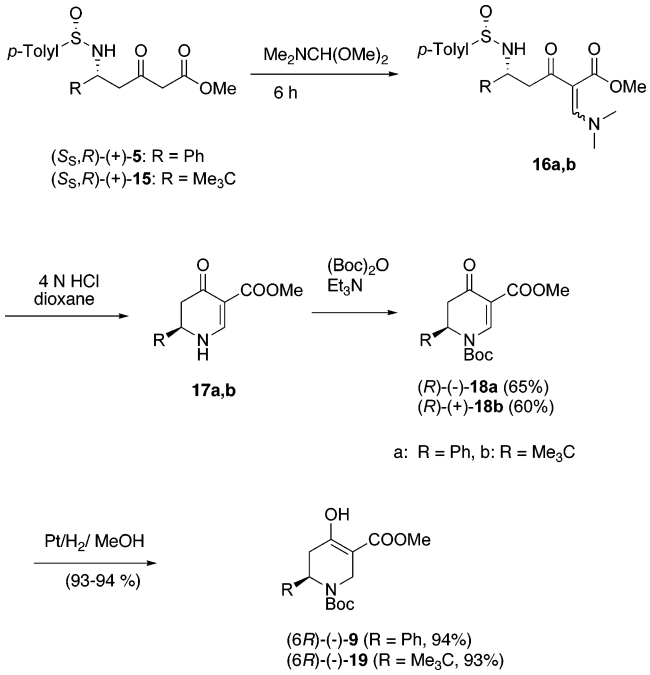
(12) Unpublished results from these laboratories.

(13) Plate, R.; Hermkens, P. H. H.; Smits, J. M. M.; Ottenheijm, H. C. J. *J. Org. Chem*. **1986**, *51*, 309.

SCHEME 3



SCHEME 4



entries 2, 5, and 6). The best yield of (−)-**9**, 50%, was obtained on a 0.15 mmol scale, with 6.0 equiv of TFA at 80 °C in toluene (Table 1, entry 3). However, attempts to increase the scale of this to maximize the yield of this product were unsuccessful (Table 1, entries 7 and 8). The best yield of pyridine (+)-**8** was 70% when the dimethoxymethane was excluded (Table 1, entry 9).

The structure of piperidone (−)-**9** and the bicyclic pyridine (+)-**8** are based on the HRMS and NMR spectra. In (−)-**9**, the enol proton appears at δ 12.0 ppm and exchanges with MeOD. The 2D-HMBC spectrum supports the bicyclic structure of (+)-**8** by the observed long-range couplings of carbon C3 to the NH proton and H9 and both CH_2 protons at C5 and C11. The substitution pattern is supported by NOE difference spectroscopy that requires separation of protons 1(NH)−6(CH, δ 5.0)−5(CH_2, δ 3.5) from the network of 11(CH_2, δ 4.21)−pyridyl H9 (δ 7.55, s)−15(2H, ortho, phenyl attached to C8). This experiment showed H9 to be placed central to H11 and H15.[14]

A plausible mechanism for the formation of the bicyclic pyridine (+)-**8** is outlined in Scheme 3. Intermolecular condensations of two molecules of δ-amino β-ketoester **10** gave **11** which cyclizes to the 4-imino piperidone **12**. Both transformations are well precedent in the chemistry of δ-amino β-ketoesters.[5−7] Next, enamine **13** cyclizes to give the bicyclic dehydropyridine **14**, which in turn undergoes air oxidation affording (+)-**8**. The fact that the highest yield of (+)-**8** results from the absence of dimethoxymethane (Table 1, entry 9), where it competes for the formation of **7**, is consistent with this mechanistic hypothesis.

δ-Amino β-Ketoester Enaminones. Enaminones (β-amino-α,β-unsaturated carbonyl compounds) are versatile structural motifs capable of reacting with either electrophiles or nucleophiles depending on the reaction conditions. As a consequence, enaminones have been widely used in the preparation of heterocycles.[15] However, to the best of our knowledge, there appears to be only a single example of their use in the asymmetric synthesis of piperidines. Here, Bousquet and co-workers employed an intramolecular Michael addition reaction of a β-ketoester enaminone to construct the piperidine ring.[16]

Treatment of (+)-**5** or (+)-**15** with 10 equiv of dimethylformamide dimethyl acetal[17] at rt for 6 h followed by removal of the solvent gave the crude δ-amino β-ketoester enaminones **16** (Scheme 4). The absorptions appearing in the proton NMR of **16** at δ 7.68 and 2.68 ppm are attributed to vinyl and *N*,*N*-dimethyl protons, respectively, and suggest that a single isomer was formed, but of unknown stereochemistry. Because of the hydrolytic instability of **16** it was used without purification and treated with 4 N HCl in dioxane to remove the *N*-sulfinyl group. Concentration gave presumably **17**. The structure of **17** is supported by the fact that when treated with $(Boc)_2O/Et_3N$ it afforded dihydropyridones **18a** and **18b** in 65 and 60% isolated yields, respectively, for the five-step one-flask sequence (Scheme 4). The formation of **17** is consistent with an intramolecular Michael addition of the free δ-amino group to the enaminone unit in **16** followed by a retro-Michael type elimination. The structure of **18** is supported by the absorption of the vinyl proton at 8.5−9.0 ppm. Hydrogenation, H_2/Pt, gave the desired piperidone/enols (−)-**9** and (−)-**19** in 94 and 93% isolated yields, respectively (Scheme 4).

Pseudodistomin B. Pseudodistomin A (**20**) and pseudodistomin B (**21**) were isolated by Kobayashi and co-workers from the Okinawan truncate *Pseruodistoma*

(14) A more detailed discussion of the NMR studies can be found in the Supporting Information.

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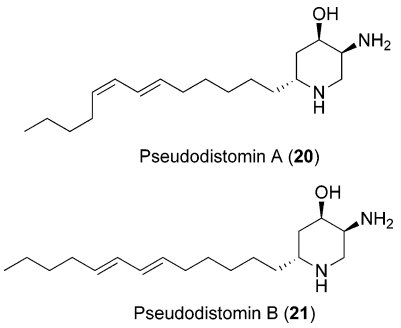
(16) Bousquet, Y.; Anderson, P. C.; Bogri, T.; Duceppe, J.-S.; Grenier, L.; Guse, I. *Tetrahedron* **1997**, *53*, 15671.

(17) For a review on formamide acetals, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

SCHEME 5



kanoko in 1987 and were the first piperidine alkaloids to be isolated from a marine source (Scheme 5).[18] These alkaloids exhibited potent cytotoxic activity against L1210 and L51178 leukemia cells, as well as inhibition of calmodulin-activated brain phosphodiesterase.[18,19] As a consequence of their important biological activity a number of asymmetric syntheses have been described.[20,21] We were particularly attracted to the synthesis of the triacetate of pseudodistomin B described by Ma and Sun.[21] Using the Curtius rearrangement, these workers developed an efficient methodology for conversion of the piperidine 4-oxo-5-carboxymethyl groups, i.e., **9** and **19**, into the *syn*-4-hydroxy-5-amino groups required for the syntheses of **20** and **21**. To construct the 2,4,5-piperidone moiety they employed a Dieckmann condensation of a derived β-amino ester. However, their condensation resulted in a 2:1 mixture of isomers that could not be separated and necessitated further synthetic transformations on the mixture. This resulted in lower overall yields.

Our formal synthesis of the triacetate of pseudodistomin B (**21**) begins with the preparation of the requisite (*R*)-(−)-*N*-(7-benzyloxyheptylidene)-*p*-toluenesulfinamide (**24**) by condensation of aldehyde **22**, prepared by oxidation of 7-benzyloxyheptan-1-ol,[22] with (*R*)-(−)-*p*-toluenesulfinamide (**23**) (Scheme 6). The sulfinimine (*R*)-**24**, isolated in 78% yield, was transformed, as previously described, into the *N*-sulfinyl δ-amino β-ketoester (R_S,*R*)-(−)-**26** by reaction of the β-amino ester (R_S,*R*)-(−)-**25** with an excess of the sodium enolate of methyl acetate.[5,7,9] Using our new δ-amino β-ketoester enaminone methodology (see above), treatment of (−)-**26** with dimethylformamide dimethyl acetal, hydrolysis, and *N*-Boc protection afforded (*R*)-(−)-**27** in 63% yield for the five-step one-flask sequence (Scheme 6). Hydrogenation of (*R*)-(−)-**27** gave the key enol intermediate (*R*)-(+)-**28** in 93% isolated yield. This enol, **28**, was the same intermediate that was obtained by Ma and Sun as an inseparable mixture of products.[21] As described by these workers, pure (*R*)-(−)-**28** was converted in our laboratory into the silyl enol ether (−)-**29**, hydrogenated, and deprotected to give (−)-**30** in 77% yield for the three steps. This completes our formal asymmetric synthesis of pseudodistomin B triacetate (Scheme 6).

Summary. Efficient and general methodology has been introduced for the asymmetric synthesis of 2,4,5-trisubstituted piperidines, a structural motif found in numerous biologically active alkaloids. This new procedure employs *N*-sulfinyl δ-amino β-ketoester enaminones **16**, a new sulfinimine derived chiral building block that is readily prepared by reaction of *N*-sulfinyl δ-amino β-ketoesters with dimethylformamide dimethyl acetal. On treatment with acid, **16** undergoes an intramolecular Michael addition followed by a retro-Michael-type elimination to afford the 2,4,5-trisubstituted piperidine in good yield for the one-pot, five-step sequence. This new methodology was illustrated with a concise formal asymmetric synthesis of the triacetate of pseudodistomin B. In the course of these studies, a novel dimerization-rearrangement of δ-amino β-ketoesters to bicyclic pyridine (+)-**8** was discovered.

Experimental Section

(S_S,*R*)-(+)-Methyl 3-oxo-5-phenyl-5-(*p*-toluenesulfinylamino)pentanoate (**5**)[5] and methyl (S_S,*R*)-(+)-6,6-dimethyl-3-oxo-5-(*p*-toluenesulfinylamino)heptanoate (**15**)[23] were prepared as previously described.

(6*R*)-(−)-4-Hydroxy-6-phenyl-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (9). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**5** (0.05 g, 0.14 mmol) in methanol (2 mL). Trifluoroacetic acid (0.065 mL, 0.84 mmol) was added, and the reaction was stirred at rt for 30 min and concentrated. The residue was dissolved in toluene (3 mL), and dimethoxymethane (0.025 mL, 0.28 mmol) was added. The solution was refluxed for 8 h, the solution was concentrated, and the residue was extracted with EtOAc (3 × 5 mL), ethyl acetate, and aqueous Na_2CO_3 (3 × 5 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated. Chromatography (hexanes/EtOAc, 1:1) afforded 0.008 g (15%) of bicyclic pyridine (+)-**9** (see below) and piperidine **7** in crude form. Crude **7** was dissolved in THF (3 mL) and treated with triethylamine (0.04 mL, 0.28 mmol) and di-*tert*-butyl dicarbonate (0.034 g, 0.15 mmol). After the reaction mixture was stirred for 3 h, aqueous NH_4Cl (5 mL) was added, and the solution was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (hexanes/EtOAc, 3:2) gave 0.024 g (50%) of a colorless oil: $[\alpha]^{20}_D$ −13.3 (*c* 0.22, $CHCl_3$); IR (neat) 1736, 1697, 1551, 1462 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9 H), 2.78 (d, J = 13.0 Hz, 1 H), 2.92 (m, 1 H), 3.30 (m, 1 H), 3.71 (s, 3 H), 4.47 (m, 1 H), 5.67 (brs, 1 H), 7.27 (m, 5 H), 12.05 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5, 28.7, 31.5, 37.1, 51.8, 80.8, 95.9, 126.8, 127.7, 128.8, 129.1, 139.4, 154.9, 168.9, 170.9; HRMS (FAB) calcd for $C_{18}H_{23}NO_5Na$ (M + Na) 356.1474, found 356.1483.

(7*R*)-(+)-(5-Oxo-2,7-diphenyl-5,6,7,8-tetrahydro[1,6]-naphthyridin-4-yl)acetic Acid Methyl Ester (8). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum,and condenser was placed (+)-**5** (0.05 g, 0.15 mmol) in methanol (3 mL), and trifluoroacetic acid (0.073 mL, 0.96 mmol) was added. After 30 min, the solvent was concentrated, the residue was dissolved in DCM (3 mL), and the solution was heated at 40 °C for 6 h. At this time the solution was cooled to rt, DCM (10 mL) was added, the solution was washed with aqueous Na_2CO_3 (10 mL), and the organic phase was dried (Na_2SO_4) and concentrated. Chromatography (hexanes/EtOAc, 3:2) gave 0.0188 g (70%) of a solid: mp 61−63 °C; $[\alpha]^{20}_D$ +70 (*c* 0.23, $CHCl_3$); IR (neat) 3200, 1736, 1659, 1555, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (m, 2 H), 3.70 (s, 3 H), 4.15 (d, J = 16.4 Hz 1 H), 4.23 (d, J =

(18) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem*. **1987**, *52*, 450.
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(21) Ma, D.; Sun, H. *J. Org. Chem*. **2000**, *65*, 6009.
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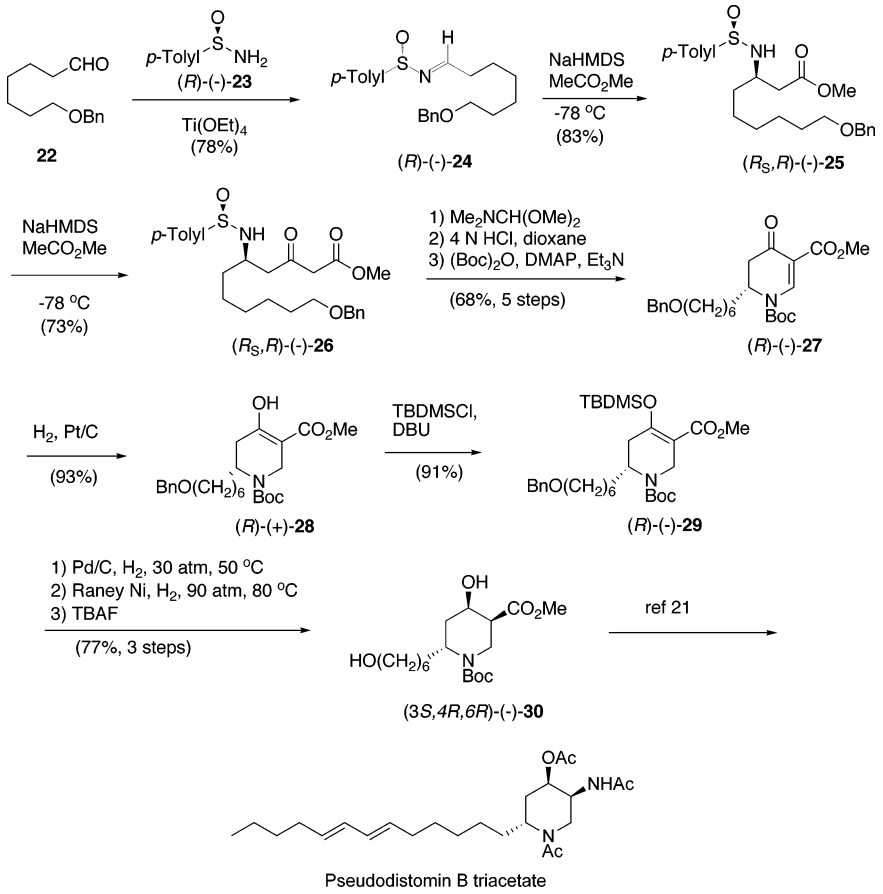
(23) Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem*. **2003**, *68*, 5147.

SCHEME 6



16.4 Hz 1 H), 4.98 (dd, J = 10.7, 5.4 Hz 1 H), 5.98 (s, 1 H), 7.32 (m, 8 H), 7.48 (s, 1 H), 7.97 (d, J = 6.5 Hz 2 H); ^{13}C NMR ($CDCl_3$) δ 40.4, 41.1, 52.2, 54.9, 120.9, 123.2, 126.4, 127.4, 128.9, 129.1, 129.2, 129.9, 138.1, 140.4, 145.8, 158.8, 159.5, 166.1, 171.2; HRMS calcd for $C_{23}H_{20}N_2O_3Na$ (M + Na) 395.1372, found 395.1382.

General Procedure for Preparing Dihydropyridones Using Dimethylforamide Dimethyl Acetal. (6*R*)-(−)-4-Oxo-6-phenyl-5,6-dihydro-4*H*-pyridine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (18a). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed β-ketoester **5** (0.9 g, 2.5 mmol) and dimethylformamide dimethyl acetal (3.4 mL, 25 mmol) in toluene (20 mL). The reaction was stirred at rt for 6 h before the solvent was removed. The residue was redissolved in 4 N HCl (in dioxane, 10 mL) and stirred at rt for 2 h. The solvent was removed in vacuo, and the residue was redissolved in acetonitrile (15 mL) with TEA (1.8 mL, 12.9 mmol), DMAP (0.06 g, 0.5 mmol), and di-*tert*-butyl dicarbonate (0.55 g, 2.5 mmol). The reaction was stirred at rt for 3 h before it was quenched with aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, concentrated, and chromatographed (hexanes/EtOAc, 2:1) to give 0.5 g (65%) of a colorless oil: $[\alpha]^{23}_D$ −146.0 (*c* 3.1, $CHCl_3$); IR (neat) 3150, 1701, 1652, 1532 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 2.81 (dd, J = 16.0, 1.5 Hz, 1 H), 3.16 (dd, J = 16.0, 7.8 Hz, 1 H), 3.81 (s, 3 H), 5.64 (d, J = 7.5 Hz, 1 H), 7.15 (m, 2 H), 7.30 (m, 3 H), 9.03 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 43.2, 52.1, 57.0, 85.8, 108.3, 125.8 128.6, 129.4, 138.4, 150.7, 151.2, 164.7, 187.5; HRMS (FAB) calcd for $C_{18}H_{21}NO_5Na$ (M + Na) 332.1498, found 332.1507.

(6*R*)-(+)-6-*tert*-Butyl-4-oxo-5,6-dihydro-4*H*-pyridine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (18b). Chromatography (hexanes/EtOAc, 2:1) gave 0.21 g (60%) of a colorless oil: $[\alpha]^{23}_D$ +113.4 (*c* 4.6, $CHCl_3$); IR (neat) 3020, 1689, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9 H), 1.51 (s, 9 H), 2.71 (m, 2 H), 3.73 (s, 3 H), 4.38 (brs, 1 H), 8.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.2, 38.1, 38.2, 52.1, 60.8, 85.5, 108.2, 151.5, 152.4, 165.0, 189.2; HRMS (FAB) calcd for $C_{16}H_{25}NO_5Na$ (M + Na) 334.1630, found 334.1638.

(6*R*)-(−)-4-Hydroxy-6-*tert*-butyl-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (19). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and hydrogen balloon were placed **18b** (0.3 g, 0.96 mmol) and Pt (5wt % on C, 0.1 g) in methanol (5 mL). After 3 h, the solution was filtered and concentrated. Chromatography (hexanes/EtOAc, 5:1) gave 0.28 g (93%) of a colorless oil: $[\alpha]^{20}_D$ −47.7 (*c* 1.6, $CHCl_3$); IR (neat) 1656, 1493, 1472 cm^{-1}; ^{1}H NMR ($CDCl_3$) (rotamer) δ 0.85 (s, 9 H), 1.40 (s, 9 H), 2.26 (m, 1 H), 2.48 (m, 1 H), 3.60 (m, 1 H), 3.68 (d, 1.4 H), 3.71 (d, 1.6 H), 4.07 (d, J = 8.1 Hz, 0.55 H), 4.28 (d, J = 8.1 Hz, 0.45 H), 4.43 (d, J = 16.8 Hz, 0.55 H), 4.63 (d, J = 16.8 Hz, 0.45 H), 11.86 (s, 0.55 H), 11.89 (s, 0.45 H); ^{13}C NMR ($CDCl_3$) (rotamer) δ 27.4, 27.7, 27.8, 28.7, 28.9, 37.1, 38.8, 39.5, 51.7, 51.8, 54.7, 56.2, 80.3, 80.4, 95.0, 95.4, 155.3, 155.7, 169.4, 170.3, 171.1,171.2; HRMS (FAB) calcd for $C_{16}H_{27}NO_5Na$ (M + Na) 336.1787, found 336.1792.

7-Benzyloxyheptanal (22). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed 7-benzyloxyheptan-1-ol[22] (1.2 g, 5.5 mmol) and PCC (3.5 g, 16.2 mmol) in dichloromethane (30 mL). After 2 h, the reaction was diluted with ether (30 mL) and filtered. The filtrate was concentrated and chromatographed (hexanes/EtOAc, 1:1) to give 1.1 g (89%) of a colorless oil: IR (neat) 3127, 2806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 4 H), 1.57 (m, 4 H), 2.36 (m, 2 H), 3.42 (t, J = 6.5 Hz, 2 H), 4.45 (s, 2 H), 7.26 (m, 5 H), 9.70 (t, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.4, 26.3, 29.3, 29.9, 44.1, 70.6, 73.3, 127.8,

128.0, 128.7, 139.1, 203.0; HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (M − H) 219.1385, found 219.1383.

(*R*)-(−)-7-Benzyloxyheptylidene-*p*-toluenesufinamide (24). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed aldehyde **22** (1.1 g, 4.8 mmol), (*R*)−(−)-**23** (0.75 g, 4.8 mmol), and $Ti(OEt)_4$ (4.5 mL, 22.5 mmol) in dichloromethane (20 mL). The reaction was stirred at room temperature for 3 h and crushed ice (10 g) was added. The reaction mixture was filtered and the filtrate was concentrated and chromatographed (hexanes:EtOAc, 10:1) to give 1.33 g (78%) of a colorless oil; $[\alpha]^{23}_D$ −158.0 (*c* 1.5, $CHCl_3$); IR (neat) 3214, 2930, 2670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (m, 3 H), 1.68 (m, 5 H), 2.48 (s, 3 H), 2.55 (m, 2 H), 3.52 (m, 2 H), 4.57 (s, 2 H), 7.38 (m, 7 H), 7.64 (m, 2 H), 8.29 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.4, 26.0, 29.0, 29.6, 35.9, 70.3, 72.9, 124.6, 127.6, 127.7, 128.4, 129.9, 138.7, 141.7, 167.3; HRMS (FAB) calcd for $C_{21}H_{27}NO_2SNa$ (M + Na) 380.1660, found 380.1667.

(S_R,*R*)-(−)-Methyl-3-(6-benzyloxyhexyl)-3-(*p*-toluenesulfinylamino)-propanoate (25). In a 250-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed NaHMDS (2.4 mL, 4.8 mmol, 2 M in THF) and methyl acetate (0.38 mL, 4.8 mmol) in ether (20 mL) at −78 °C. The solution was stirred at this temperature for 1 h before a solution of sulfinimine (−)-**24** (1.14 g, 3.2 mmol) in ether (15 mL) was added slowly. After 1 h the reaction was quenched with aqueous NH_4Cl (20 mL) and the solution was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), and concentrated. Chromatography (hexanes:EtOAc, 2:1) gave 1.15 g (83%) of a colorless oil; $[\alpha]^{23}_D$ −57.9 (*c* 0.51, $CHCl_3$); IR (neat) 3280, 2870, 1789 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (m, 10 H), 2.33 (s, 3 H), 2.53 (m, 2 H), 3.40 (t, J = 6.6 Hz, 2 H), 3.59 (s, 3 H), 3.62 (m, 1 H), 4.45 (m, 3 H), 7.24 (m, 7 H),7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 26.3, 26.4, 29.5, 30.0, 36.1, 40.8, 52.0, 53.0, 70.7, 73.2, 125.9, 127.8, 128.0, 128.7, 129.9, 139.0, 141.6, 142.8, 172.3; HRMS (FAB) calcd for $C_{20}H_{33}NO_4SNa$ (M + Na) 454.2028, found 454.2024.

(R_S,R)-(−)-Methyl-3-oxo-5-(6-benzyloxyhexyl)-5-(*p*-toluenesulfinylamino)pentanoate (26). In a 250-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum and argon balloon was placed NaHMDS (12.3 mL, 12.3 mmol, 1 M in THF,) and methyl acetate (0.98 mL, 12.3 mmol) in THF (30 mL) at −78 °C. The solution was stirred at this temperature for 1 h before a solution of (−)-**25** (1.06 g, 2.46 mmol) in THF (20 mL) was added slowly. After 7 h at −78 °C the reaction mixture was quenched with aqueous NH_4Cl (20 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4, concentrated, and chromatographed (hexanes: EtOAc, 1:1) to give 0.85 g (73%) of a colorless oil; $[\alpha]^{23}_D$ −49.6 (*c* 1.1, $CHCl_3$); IR (neat) 3170, 2659, 1896 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (m, 6 H), 1.47 (m, 4 H), 2.26 (s, 3 H), 2.72 (t, J = 5.2 Hz, 2 H), 3.27 (s, 2 H), 3.32 (t, J = 6.6 Hz, 2 H), 3.53 (m, 1 H), 3.57 (s, 3 H), 4.24 (d, J = 9.2 Hz, 1 H), 4.36 (s, 2 H), 7.16 (m, 7 H),7.41 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.7, 26.4, 29.4, 30.0, 36.1, 49.1, 49.9, 52.4, 52.6, 70.7, 73.2, 125.9, 127.8, 127.9, 128.7, 129.9, 139.0, 141.6, 142.7, 167.7, 201.8; HRMS (FAB) calcd for $C_{26}H_{35}NO_5SNa$ (M + Na) 496.2134, found 496.2150.

(*R*)-(−)-6-(6-Benzyloxyhexyl)-4-oxo-5,6-dihydro-4*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (27). In a 25-mL single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (−)-**26** (0.31 g, 0.65 mmol) and dimethylformamide dimethylacetal (0.87 mL, 6.5 mmol) in toluene (5 mL). The reaction was stirred at room temperature for 5 h, concentrated, and the residue was dissolved in 4 N HCl (in dioxane, 6 mL). After stirring for 2 h the solvent was removed in vacuo, the residue was dissolved in acetonitrile (5 mL) containing TEA (0.27 mL, 1.9 mmol), DMAP (0.016 g, 0.13 mmol), and di-*tert*-butyl dicarbonate (0.28 g, 1.28 mmol). The reaction mixture was stirred at room temperature for 6 h and quenched with aqueous NH_4Cl (10 mL). The solution was extracted with EtOAc (3 × 10 mL), the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, concentrated. Chromatography (hexanes:EtOAc, 1:1) afforded 0.197 g (68%) of colorless oil. Chromatography (hexanes: EtOAc, 1:1) afforded 0.24 g (68%) of colorless oil; $[\alpha]^{23}_D$ −26.1 (*c* 1.3, $CHCl_3$); IR (neat) 3210, 1891, 1654, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (m, 7 H), 1.56 (s, 9 H), 1.61 (m, 3 H), 2.52 (dd, J = 15.8, 1.8 Hz, 1 H), 2.79 (dd, J = 15.8, 6.3 Hz, 1 H), 3.44 (t, J = 6.8 Hz, 2 H), 3.81 (s, 3 H), 4.49 (s, 2 H), 4.52 (m, 1 H), 7.31 (m, 5 H), 8.76 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.3, 28.2, 29.4, 29.9, 31.1, 40.5, 52.1, 53.9, 70.5, 73.2, 85.4, 107.5, 127.8, 127.9, 128.7, 139.0, 150.4, 150.7, 164.9, 188.7; HRMS (FAB) calcd for $C_{25}H_{35}NO_6Na$ (M + Na) 468.2362, found 468.2374.

(6*R*)-(+)-6-(6-Benzyloxyhexyl)-4-hydroxy-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (28). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and hydrogen balloon was placed (−)-**27** (0.177 g, 0.40 mmol) and Pt (0.0015 g, 5wt % on carbon) in methanol (5 mL). After 30 min, the solution was filtered, concentrated, and chromatographed (hexanes:EtOAc, 5:1) to give 0.167 g (93%) of a colorless oil; $[\alpha]^{23}_D$ +52.9 (*c* 0.33, $CHCl_3$); IR (neat) 1798, 1656, 1548, 1482 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (m, 6 H), 1.47 (s, 9 H), 1.57 (m, 4 H), 2.09 (m, 1 H), 2.65 (m, 1 H), 3.48 (m, 3 H), 3.77 (s, 3 H), 4.41 (m, 4 H), 7.31 (m, 5 H), 12.1 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.5, 28.6, 28.7, 28.8, 29.5, 30.1, 31.9, 51.9, 70.7, 73.2, 80.3, 127.8, 128.0, 128.7, 139.1, 155.1, 171.3; HRMS (FAB) calcd for $C_{25}H_{37}NO_6Na$ (M + Na) 470.2519, found 470.2524.

(*R*)-(+)-6-(6-Benzyloxyhexyl)-4-(*tert*-butyldimethylsilanyloxy)-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (29). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed (+)-**28** (0.026 g, 0.058 mmol), TBDMSCl (0.018 g, 0.12 mmol), and DBU (0.018 mL, 0.12 mmol) in DCM (2 mL). The reaction was stirred at rt for 30 min and quenched with aqueous NH_4Cl (3 mL). The organic phase was dried over Na_2SO_4 and concentrated. Chromatography (hexanes/EtOAc, 5:1) gave 0.03 g (91%) of a colorless oil: $[\alpha]^{23}_D$ +19.1 (*c* 0.71, $CHCl_3$); IR (neat) 3124, 1806, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 3 H), 0.18 (s, 3 H), 0.95 (s, 9 H), 1.31 (m, 7 H), 1.46 (s, 9 H), 1.61 (m, 4 H), 1.94 (m, 1 H), 2.59 (m, 1 H), 3.28 (t, J = 6.6 Hz, 2 H), 3.56 (m, 1 H), 3.70 (s, 3 H), 4.34 (brs, 1 H), 4.49 (s, 2 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −3.4, −3.3, −3.2, 18.7, 25.8, 26.0, 26.5, 26.6, 28.8, 29.6, 30.1, 31.9, 51.3, 70.7, 73.2, 80.2, 127.8, 128.0, 128.7, 139.1, 155.1; HRMS (FAB) calcd for $C_{31}H_{51}NO_6SiNa$ (M + Na) 584.3383, found 584.3383.

(3*S*,4*R*,6*R*)-(−)4-Hydroxy-6-(6-hydroxyhexyl)piperidine-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-Methyl Ester (30). In a 250-mL Parr 4601 high-pressure/high-temperature vessel were placed **29** (0.06 g, 0.107 mmol) and 10% Pd/C (0.1 g) in EtOAc (15 mL). The solution was stirred under 30 atm of H_2 at 50 °C for 24 h. At this time, the solution was filtered and to the filtrate was added Raney Ni (0.2 g). The solution was stirred under 90 atm of H_2 at 80 °C for 24 h. At this time, the solution was filtered, the filtrated was concentrated, and the residue was dissolved in THF (2 mL). To the solution was added TBAF (0.155 mL, 0.155 mmol, 1 M solution in THF) at 0 °C, and the reaction mixture was slowly warmed to rt and stirred for 30 min. At this time, the reaction was quenched with 1 N HCl (4 mL) and the solution was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Chromatography gave 0.03 g (77%) of a colorless oil: $[\alpha]^{23}_D$ −18.6 (*c* 1.2, $CHCl_3$), [lit.[21] $[\alpha]^{23}_D$ −17.3 (*c* 1.44, CH_3Cl)]; IR (neat) 3304, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (m, 6 H), 1.43 (s, 9 H), 1.60 (m, 4 H), 1.80 (m, 1 H), 1.98 (m, 1 H), 2.85 (brs, 1 H), 2.96 (dd, J = 14.5, 3.5 Hz, 1 H), 3.34 (brs, 1 H), 3.63 (t, J =

6.5 Hz, 2 H), 3.72 (s, 3 H), 3.96 (m, 1 H), 4.32 (brs, 1 H), 4.54 (d, $J = 14.0$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.0, 26.7, 28.7, 29.4, 30.1, 30.8, 33.0, 34.5, 40.1, 45.8, 51.0, 52.2, 63.2, 66.2, 80.0, 154.9, 173.6; HRMS (FAB) calcd for $C_{18}H_{33}NO_6Na$ (M + Na) 382.2206, found 382.2203.

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

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