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Highly Efficient *O*-Glycosylations with *p*-Tolyl Thioribosides and *p*-TolSOTf

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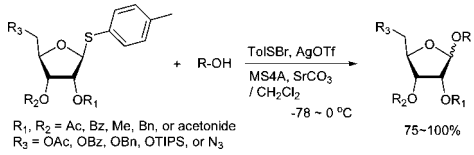

A wide variety of *p*-tolyl thioriboside donors are examined for *O*-ribosylations of *primary* and *secondary* alcohols. *p*-Tolylsulfenyl trifluoromethanesulfonate (*p*-TolSOTf) is very effective in promoting *O*-ribosylations with *p*-tolyl thioriboside; all reactions are completed within 1−15 min to provide the desired products in good yield with reliable α/β selectivity. A wide range of functional groups are tolerated under these conditions. The described *O*-ribosylation conditions are very useful for the generation of ribosaminouridine library molecules in solution or on polymer support.

The 5-deoxy-5-aminoribose moiety of ribosaminouridine antibiotics (i.e., muraymycin, liposidomycin, caprazamycin, and FR-900493) has been considered as an important functional group to exhibit excellent antibacterial activities.[1] These antibiotics are known to interfere with the enzyme involved in the committed step of peptidoglycan biosynthesis, MraY, which catalyzes the transformation of UDP-*N*-acylmuramyl-L-alanyl-γ-D-glutamyl-*meso*-diaminopimelyl-D-alanyl-D-alanine (Park's nucleotide) to prenylpyrophosphoryl-*N*-acylmuramyl-L-Ala-γ-D-glu-*meso*-DAP[2]-D-Ala-D-Ala (lipid I), and are nontoxic or less toxic in vivo. Thus, MraY has been a target of interest for the discovery of novel antimycobacterial agents.[3] However, medicinal chemistry programs of these natural products with an aim to improve the efficacy including pharmacokinetics are hampered by a limited number of modification reactions which can selectively modify the desired positions of such complex molecules.[4] In addition, one of the drawbacks of performing medicinal chemistry with these complex antibiotics is the requirement for the fermentation of the natural product starting materials.[5]

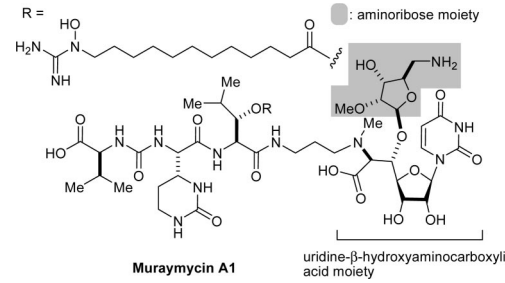

FIGURE 1. Representative structure of ribosaminouridine antibiotics.

In our ongoing effort to define the minimum structure requirement of ribosaminouridine MraY inhibitors of natural product origin to exhibit equal biological activity,[6] we envisioned synthesizing a library of ribosaminouridine molecules in solution or on polymer support.[7] Because the structural diversity of ribosaminouridine antibiotics is observed not only in the lipid moiety (R group in Figure 1) but also at the 2-position of aminoribose moiety (i.e., methyl or sulfonyl group), it is desired to develop a versatile and robust ribosylation method which is also amenable to glycosylations on polymer support.[8]

Although numerous examples of *N*-glycosylations of purine or pyrimidine bases with furanose derivatives have been reported,[9] *O*-ribosylation has rarely been discussed in the literature. Recently, Merrer and co-workers reported *O*-ribosylations of *primary* alcohols using bromo- or fluororibosides with the established promoters such as AgOTf or $SnCl_2/AgClO_4$.[10] Reaction rates for *O*-ribosylations with 1-haloriboside are very slow (6−36 h), and in our hands under these conditions, *O*-ribosylations of the *secondary* alcohols resulted in unsatisfactory yields of 15−65%. In addition, because of the limited accessibility of 1-haloribosides, it is difficult to diversify ribosaminouridine library molecules by *O*-ribosylations with these methods. In this paper, we wish to report expeditious

(1) Dini, C. *Curr. Top. Med. Chem.* **2005**, *5*, 1221.
(2) DAP: (2*R*,6*S*)-2,6-diaminoheptanedioic acid.
(3) van Heijenoort, J. *Glycobiology* **2001**, *11*, 25R.
(4) (a) Corre, L. L.; Gravier-Pelletier, C.; Merrer, Y. L. *Eur. J. Org. Chem.* **2007**, 5386. (b) Hirano, S.; Ichikawa, S.; Matsuda, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1854. (c) Hotoda, H.; Daigo, M.; Furukawa, M.; Murayama, K.; Hasegawa, C. A.; Kaneko, M.; Muramatsu, Y.; Ishii, M. M.; Miyakoshi, S.; Takatsu, T.; Inukai, M.; Kakuta, M.; Abe, T.; Fukuoka, T.; Utsui, Y.; Ohya, S. *Bioorg. Med. Chem. lett.* **2003**, *13*, 2833.
(5) No efficient chemical synthesis of ribosaminouridine natural products which can be performed medicinal chemistry has been reported.
(6) For synthetic effort towards identification of the minimum structure requirement of liposidomycins, see: Dini, C.; Drochon, N.; Feteanu, S.; Guillot, J. C.; Peixoto, C.; Aszodi, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 529.
(7) Kurosu, M.; Narayanasamy, P.; Crick, D. C. *Heterocycles* **2007**, *72*, 339.
(8) In mycobacterial growth inhibitory and enzymatic assays against MraY of representative uridine-β-hydroxyaminocarboxylic acid derivative, it was realized that the molecules which do not possess the aminoribose group significantly lowered mycobacterial growth inhibitory activity. Thus, it is important to retain the aminoribose (highlighted in Figure 1) or its equivalent in MraY inhibitors of uridine-β-hydroxyaminocaroxylic acid analogues.
(9) (a) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (b) Townsend, L. B. In *Nucleoside Analogues: Chemistry, Biology and Medical Applications*; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York, 1979; p 193. (c) Reese, C. B. *Tetrahedron* **1978**, *34*, 3143.
(10) Ginistry, M.; Gravier-Pelletier, C.; Merrer, Y. L. *Tetrahedron: Asymmetry* **2006**, *17*, 142.

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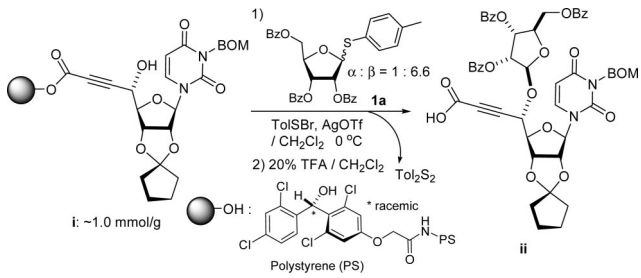
SCHEME 1. Screening of a Promoter for 1 Using the Immobilized Propargyl Alcohol on the Polymer Resin i



O-ribosylations of *primary* and *secondary* alcohols with a wide variety of *p*-tolyl thioriboside donors and *p*-TolSOTf that would be very useful to synthesize a library of ribosaminouridine molecules.[11]

Because thioglycosides (1) can conveniently be synthesized via acid-catalyzed thioglycosylations of 1-*O*-acetylglycoside and (2) exhibit excellent chemical stabilities against acids and bases, the anomeric thioethers have been widely utilized as a temporary protecting group of anomeric positions as well as glycosyl donors.[12] However, a choice of promoter requires careful consideration when using less electrophilic thioglycosides; in some cases, no activation or very slow reaction rate was observed using conventional thiophilic reagents.[13] In order to identify an effective thiophilic reagent for *O*-ribosylations, we first screened thiophilic reagents using an anomeric mixture (α/β = 1:6.6) of *p*-tolyltribenzoyl thioglycosides **1a** and the immobilized propargyl alcohol on the polymer resin **i**.[14] As a result of extensive reaction screenings, it was found that *p*-TolSOTf in situ generated from *p*-TolSBr[15] and AgOTf provided the β-*O*-ribosylated product **ii** in near-quantitative yield within 15 min at 0 °C;[16] **ii** was characterized after cleavage from the polymer resin with 20% TFA. Significantly, even in the presence of a large excess of the promoters (>10 equiv), all functional groups (acetal, alkyne, alkene, and BOM protecting group) were intact. It is worth mentioning that the other conditions tested (i.e., NIS, NIS/TfOH, NIS/AgOTf, and NIS/$AgBF_4$)[17] provided **ii** in 0−15% yields together with a significant amount of byproduct.[18]

To investigate how effectively *p*-TolSOTf can promote glycosylations of a wide range of *p*-tolylthioribosides, we synthesized the donor ribosides **1b**−**n**, and the conditions developed for an *O*-ribosylation on the polymer resin (Scheme 1) were applied to *primary* and *secondary* alcohols in solution. All reactions were conducted with donor (2 equiv against acceptor), *p*-TolSOTf (1 equiv against donor), and MS (4 Å) (2 times the weight of donor)[19] in CH_2Cl_2 in the presence or absence of $SrCO_3$.[20] The representative *O*-ribosylations using these conditions are summarized in Table 1. The reactions of the *primary* alcohols **2a**−**e** with tri-*O*-acyl riboside **1a** or **1b** at 0 °C provided the corresponding β-glycosides **3a**−**f** exclusively with greater than 85% yield within 1−5 min (entries 1−6). It was realized that *p*-TolSOTf, which colors blue in CH_2Cl_2, could be generated even at −78 °C[21] and could also activate **1a** and **1b** at the same temperature without a noticeable decrease in the reaction rate. Because chemical modifications of the 5-position of 5-deoxy-5-aminoribose in ribosaminouridine antibiotics is important to improve in vitro and in vivo efficacy, glycosylations of the acceptor **2e** with the 5-TIPS-protected thioribose **1c** and 5-azido-5-deoxythioriboside **1d**, whose 5-positions can easily be diversified after glycosylations, were evaluated. Under the buffered conditions (condition B in Table 1), the azide and silyl groups in the ribosyl donors were intact (entries 7 and 8). The *primary* and *secondary* donor alcohols (i.e., alkanols, alkynols, and homoallylic alcohols)[22] were ribosylated with the donors **1a**−**d** to furnish the β-glycosides in greater than 80% yield; limited examples of the reactions of the *secondary* alcohols (i.e., **2f**) are shown in Table 1 (entries 19−21).[22] However, *primary* and *secondary* allylic alcohols (i.e., 5-phenylpent-1-en-3-ol) were not applicable to these conditions due probably to their low nucleophilicity. Ribosylations of propargyl alcohol with the ether-protected thioribosides **1e**−**g** (entries 9−11) provided a mixture of α/β glycosides (5−6.6/1) in 75−90% yield. Thus, a synthetically useful level of α-selectivity in *O*-ribosylations was observed by using the ether protecting groups. Glycosylations of propargyl alcohol with the acetonide protected thioribosides **1h**−**j** (entries 12−14) provided a 1:1.1 (α/β) mixture of the corresponding products regardless of structure of the 5-position of **1h**−**j**. As seen in muraymycins (Figure 1), an alkylation is observed at the 2-position of the aminoribose unit. To study the effect of the 3-*O*-acyl group in the 2-*O*-methylated thioglycosides, glycosylations of propargyl alcohol with **1k**−**n** (entries 15−18) were examined. The 3-*O*-acetyl group in **1k**−**n** was effective in reversing the selectivity; the reactions with **1k** or **1l** gave a 1:3 mixture of the α- and β-ribosides. The 3-*O*-benzoyl-protected donors **1m** or **1n** improved α/β-selectivity (α/β = 1:5.5). These selectivities observed at 0 °C were not dramatically enhanced by lowering the reaction temperatures (i.e., −78 °C); the α/β selectivity was increased to 1:6.5 for **1m**. The glycosylations of **2f**, a versatile intermediate for the generation of ribosaminouridine libraries, with **1m** or **1n** gave identical selectivities (α/β = 1:5.5) observed for the *primary* alcohol. Similarly, the reactions of **2f** with the 3-*O*-acetate, **1k** or **1l**, provided an anomeric mixture (α/β = 1:2.5) of the glycosides (Scheme 2). Mechanistically, the ribosyl carbenium ion generated by *p*-TolSOTf would first be stabilized by the formation of an intimate ion pair[23] with triflate ion and undergoes a pseudo-5-membered ring formation when the 2-*O*-acyl ribosyl donor is applied. These processes must proceed prior to the glycosylation step. Although an anchimeric as-

(11) For ther potential glycosylations with ribose derivatives, see: (a) Garcia, B. A.; Poole, J. A.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597. (b) Knapp, S.; Shieh, W.-C. **1991**, *32*, 3627.

(12) (a) Ekelof, K.; Garegg, P. J.; Olsson, L.; Oscarson, S. *Pure Appl. Chem.* **1997**, *69*, 1847. (b) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.

(13) For an example of the nonsusceptible thioglycoside against NIS/TfOH, see: Li, K.; Kurosu, M. *Heterocycles* **2008**, *76*, 455.

(14) Kurosu, M.; Biswas, K.; Crick, D. C. *Org. Lett.* **2007**, *9*, 1141.

(15) p-TolSBr was generated by mixing a 1:1 ratio of $(p\text{-TolS})_2$ and Br_2 in $ClCH_2CH_2Cl$, and this was stable over 1 month at rt.

(16) For a discussion of the utility of *p*-TolSCl/AgOTf for glycosylations with the thiopyranosides, see: (a) Huang, X.; Huang, L.; Wang, H.; Ye, X-S. *Angew. Chem. Int. Ed* **2004**, *43*, 5221.

(17) Kaeothip, S.; Pornsuriyasak, P.; Demchenko, A. V. *Tetrahedron. Lett.* **2008**, *49*, 1542.

(18) We also examined the effect of MeSOTf for this reaction. However, trace amounts of the desired product were isolated; see: (a) Kurosu, M.; Kitagawa, I. *J. Carbohydr. Chem.* **2006**, *25*, 427. (b) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, C13.

(19) MS (4 Å) is not indispensable for these reactions. In order not to obtain inconsistent results caused by adventitious water, two times the weight of MS was added in all reactions.

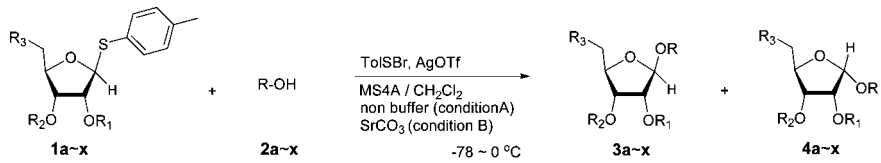
(20) $SrCO_3$ was applied as a buffer of the reactions. Addition of $SrCO_3$ was effective, especially in the reaction with the silyl group containing donors. 2,6-Di-*tert*-butylpyridine was also effective, but the reaction rate was diminished.

(21) There is a short half-life (ca. 5−15 min) for *p*-TolSOTf at rt.

(22) For other examples of ribosylations with *primary* and *secondary* alcohols, see the Supporting Information.

(23) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 328.

TABLE 1. Representative *O*-Ribosylations of Alcohols Using *p*-Tolyl thioglycosides and *p*-TolSOTf[a]

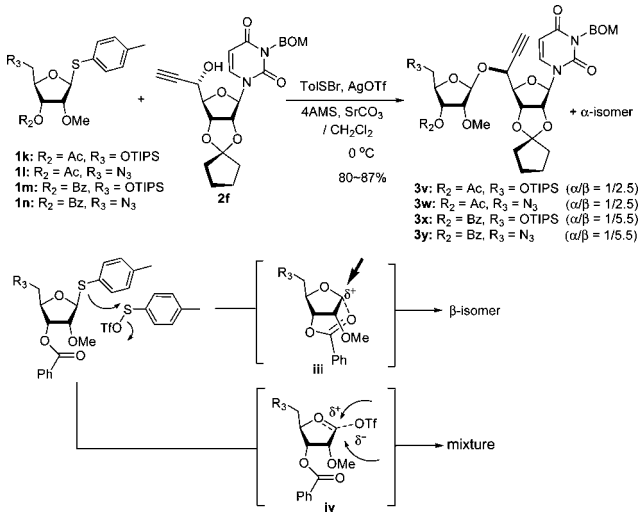


Entry	Donor	Acceptor	Temperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (**4**/**3**)[b]
1	**1a:** R_1, R_2 = Bz, R_3 = OBz	**2a**	-78~0	A	**3a:** R_1, R_2 = Bz, R_3 = OBz	98	0/1
2	**1b:** R_1, R_2 = Ac, R_3 = OAc				**3b:** R_1, R_2 = Ac, R_3 = OAc	98	0/1
3	**1a**	**2b**	-78~0	A	**3c**	100	0/1
4	**1a**	**2c**: R= Boc	-78~0	B	**3d**: R= Boc	95	0/1
5		**2d**: R= Fomc			**3e**: R= Fomc	98	0/1
6	**1a:** R_3 = OBz	**2e**	0	B	**3f:** R_3 = OBz	98	0/1
7	**1c:** R_3 = OTIPS				**3g:** R_3 = OTIPS	95	0/1
8	**1d:** R_3 = N_3				**3h:** R_3 = N_3	85	0/1
9	**1e:** R_1, R_2 = Bn, R_3 = OBn	**2b**	0	B	**4i:** R_1, R_2 = Bn, R_3 = OBn	90	6.6/1
10	**1f:** R_1, R_2 = Bn, R_3 = OTIPS				**4j:** R_1, R_2 = Bn, R_3 = OTIPS	75	6.0/1
11	**1g:** R_1, R_2 = Me, R_3 = OTIPS				**4k:** R_1, R_2 = Me, R_3 = OTIPS	78	5.0/1
12	**1h:** R_3 = OBz	**2b**	0	B	**3l:** R_3 = OBz	95	1/1.1
13	**1i:** R_3 = OTIPS				**3m:** R_3 = OTIPS	85	1/1.1
14	**1j:** R_3 = N_3				**3n:** R_3 = N_3	80	1/1.1
15	**1k:** R_2 = Ac, R_3 = OTIPS	**2b**	0	B	**3o:** R_2 = Ac, R_3 = OTIPS	85	1/3.0
16	**1l:** R_2 = Ac, R_3 = N_3				**3p:** R_2 = Ac, R_3 = N_3	90	1/3.0
17	**1m:** R_2 = Bz, R_3 = OTIPS				**3q:** R_2 = Bz, R_3 = OTIPS	85	1/5.5
18	**1n:** R_2 = Bz, R_3 = N_3				**3r:** R_2 = Bz, R_3 = N_3	90	1/5.5
19	**1a:** R_3 = OBz	**2f**	0	B	**3s:** R_3 = OBz	90	0/1
20	**1c:** R_3 = OTIPS				**3t:** R_3 = OTIPS	80	0/1
21	**1d:** R = N_3				**3u:** R_3 = N_3	90	0/1

[a] 2 equiv of donors against acceptor were used in all reactions. [b] Ratio was established by ^{1}H NMR analysis or based on isolated yield.

sistance by the 3-*O*-acyl group to form a pseudo-6-membered ring (**iii** in Scheme 2) has not been proven theoretically, the data summarized in Table 1 (e.g., entry 11 vs 17) clearly indicate that the 3-*O*-acyl carbonyl group is responsible for *β*-selective glycosylations. It is speculated that the formation of a pseudo-6-membered ring is a slower process than that of a 5-membered

SCHEME 2. Glycosylations of 2f with the thioribosides 1k−n



ring. Thus, nonselective glycosylation of an intermediate **iv** may compete with β-selective glycosylation (through **iii**) to provide an α/β anomeric mixture. The 3-*O*-benzoyl group seems to be stereoelectronically more favored than the 3-*O*-acetyl group to participate in anchimeric assistance in ribosylations (Scheme 2).[24]

In conclusion, thioribosides were, for the first time, generalized for *O*-ribosylations using *p*-TolSOTf.[25] *p*-TolSOTf can be generated by a mixing *p*-TolSBr and AgOTf in CH_2Cl_2 at −78 to 0 °C and has a short half-life (ca. 15 min) at 0 °C. However, the reaction rate of *O*-ribosylations under these conditions is very fast; all reactions summarized in Table 1 were completed within 1−15 min. The 2-*O*-acyl group is an important factor to obtain β-selective ribosylation product exclusively. The anchimeric assistance of the 3-*O*-acyl group may furnish β-selective ribosylations with 2-*O*-alkyl thioribosides. The ether-protected thioglycosides provided useful levels of α-selectivities (i.e., α/β = 6.6/1 for benzyl ether). The 2,3-acetonide-protected thioglycosides give rise to a 1:1.1 (α/β) anomeric mixture of ribosides. Most importantly, *p*-TolSOTf is applicable to substrates possessing a wide variety of functional groups such as alkyne, alkene, and commonly utilized protecting groups in multiple step syntheses (i.e., silyl, ketal, and ether protecting groups, and N_3 group). Moreover, the conditions reported here are applicable to *O*-ribosylations on the polymer-supported resin (Scheme 1). The 2- and 5-positions of aminoribose moiety of ribosaminouridine library molecules can be diversified by using the thioriboside donors summarized in Table 1 and their related structure of molecules. The generation of diverse structures of ribosaminouridine libraries and biological evaluations of these library molecules will be reported elsewhere.

(24) For the other mechanistic considerations, see Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195.

(25) For applications of thiohlycoside for arabinosylation and galactofuranosylation reactions see, (a) Pathak, A. K.; Pathak, V.; Seitz, L.; Gurcha, S. S.; Besra, G. S.; Riordan, J. M.; Reynolds, R. C. *Bioorg. Med. Chem.* **2007**, *15*, 5629. (b) Joe, M.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885.

Experimental Section

Typical Procedure for *O*-Ribosylation with 1a. A mixture of **1a** (2.0 equiv), alcohols (1.0 equiv), MS (4 Å), AgOTf (2.0 equiv), and $SrCO_3$ (4.0 equiv; conditions B) in CH_2Cl_2 (0.1−0.2 M) was stirred at rt for 15 min. The reaction mixture was cooled 0 °C, and *p*-TolSBr (2.0 M in $ClCH_2CH_2Cl$, 2.0 equiv) was added. After 1−15 min, the reaction mixture was quenched with Et_3N (5.0 equiv), and the resulting mixture was filtered through a SiO_2 plug. Purification by silica gel chromoatography (hexanes/EtOAc) provided the desired products. $SrCO_3$ was excluded for conditions A.

Propargyl 5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (3n and 4n). 3n (β isomer): $[\alpha]^{20}_D = +78.4$ (*c* 0.5 in $CHCl_3$); IR (film) 2102, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.65 (dd, J = 6.0 Hz, 18.9 Hz, 2H), 4.32 (t, J = 7.2 Hz, 1H), 4.26 (dd, J = 1.2, 2.4 Hz, 1H), 4.24 (dd, J = 1.2, 2.1 Hz, 1H), 3.46 (dd, J = 7.8, 12.6 Hz, 1H), 3.30 (dd, J = 6.9, 12.6 Hz, 1H), 2.46 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.1, 107.1, 85.9, 85.4, 82.2, 75.2, 54.8, 53.8, 26.6, 25.1; HRMS (ESI) calcd for $C_{11}H_{15}N_3NaO_4$ $(M + Na)^+$ 276.0960, found 276.0960. **4n** (α isomer): $[\alpha]^{20}_D = -16.0$ (*c* 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (d, J = 4.8 Hz, 1H), 4.73 (dd, J = 4.8, 7.2 Hz, 1H), 4.55 (dd, J = 3.6 Hz, 7.2 Hz, 1H), 4.32 (dd, J = 2.4, 4.2 Hz, 2H), 4.27 (m, 1H), 3.55 (dd, J = 4.0, 13.2 Hz, 1H), 3.36 (dd, J = 4.4, 16.0 Hz, 1H), 2.39 (t, J = 2.4 Hz, 1H), 1.55 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ116.2, 99.8, 81.2, 81.2, 80.7, 75.0, 55.1, 52.6, 26.2, 26.1; HRMS (ESI) calcd for $C_{11}H_{15}N_3NaO_4$ $(M + Na)^+$ 276.0960, found 276.0962.

Acknowledgment. This paper is dedicated to the memory of Professor Albert I. Meyers, an inspirational scientist. We thank the National Institutes of Health and Colorado State University for generous financial support.

Supporting Information Available: Experimental procedures, full characterization data for new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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