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Expedient Synthesis of the α-*C*-Glycoside Analogue of the Immunostimulant Galactosylceramide (KRN7000)

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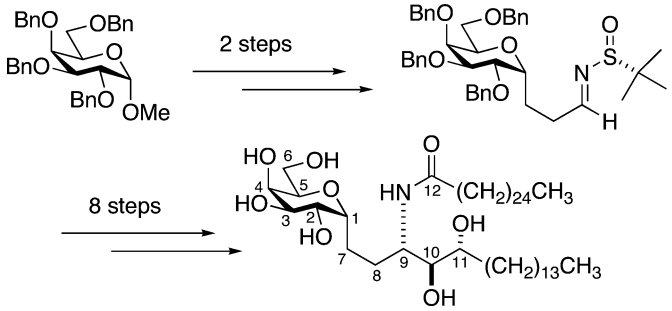
ABSTRACT



Key reactions in a concise synthesis of an α-*C*-galactosylceramide analogue of KRN7000 include a diastereoselective alkenylalane addition to an *N*-*tert*-butanesulfinyl imine and the use of an epoxidation/carbamate ring opening sequence to install the aminodiol stereotriad.

Glycolipids have been a target of increasing interest in immunostimulant research since the discovery of the therapeutic potential of α-galactosylceramides, particularly KRN7000 (**1**).[1] Impressive activities have been recorded against various disease models, including cancer,[2a] maleria,[2b] and hepatitis B.[2c] The current model for the mode of action of **1** involves sequential attachment to CD1d receptors on antigen-presenting cells and natural killer T cells, resulting in disease suppression.[3] Of the various analogues of **1** that have been prepared, the α-*C*-galactosylceramide analogue **2** developed by Franck et al. has shown a spectacular increase in potency: a 1000-fold enhancement of **2** over **1** was found in a mouse malaria assay, and a 100-fold activity increase was detected in a mouse melanoma model.[4] The initial synthesis of **2** by Franck and co-workers involved the use of the Ramberg−Baecklund reaction as the key step, and this approach was subsequently improved through the use of olefin cross-metathesis.[4b] Other groups have developed alternative routes that allow for facile analogue preparation, including the synthesis of the *β*-*C*-galactosylceramide; however, these approaches are plagued by poor stereoselectivity in installing the amino-diol stereotriad of **2**.[5]

While investigating our cationic zirconocene addition to glycal epoxides,[6] it became clear that the inclusion of

(1) (a) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771. (b) Morita, M.; Motoki, K.; Akimoto, K.; Natori, T.; Sakai, T.; Sawa, E.; Yamaji, K.; Koezuka, Y.; Kobayashi, E.; Fukushima, H. *J. Med. Chem.* **1995**, *38*, 2176. (c) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J. Org. Chem.* **2004**, *69*, 1174.

(2) (a) Hayakawa, Y.; Rovero, S.; Forni, G.; Smyth, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 9464. (b) Gonzalez-Aseguinolaza, G.; de Oliveira, C.; Tomaska, M.; Hong, S.; Bruna-Romero, O.; Nakayama, T.; Taniguchi, M.; Bendelac, A.; Van Kaer, L.; Koezuka, Y.; Tsuji, M. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 8461. (c) Kakimi, K.; Guidotti, L. G.; Koezuka, Y.; Chisari, F. V. *J. Exp. Med.* **2000**, *192*, 921.

(3) Brigl, M.; Brenner, M. B. *Annu. Rev. Immunol.* **2004**, *22*, 817.

(4) (a) Yang, G.; Schmieg, J.; Tusji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3818. (b) Chen, G.; Schmieg, J.; Tsuji, M.; Frank, R. W. *Org. Lett.* **2004**, *6*, 4077. (c) Franck, R. W.; Tsuji, M. *Acc. Chem. Res.* **2006**, in press. (d) Chen, G.; Chien, M.; Tsuji, M.; Franck, R. W. *ChemBioChem* **2006**, *7*, 1017.

(5) (a) Toba, T.; Murata, K.; Yamamura, T.; Miyake, S.; Annoura, H. *Tetrahedron Lett.* **2005**, *46*, 5043. (b) Chaulagain, M. R.; Postema, M. H. D.; Valeriote, F.; Pietraszkewicz, H. *Tetrahedron Lett.* **2004**, *45*, 7791.

(6) Wipf, P.; Pierce, J. G.; Zhuang, N. *Org. Lett.* **2005**, *7*, 483.

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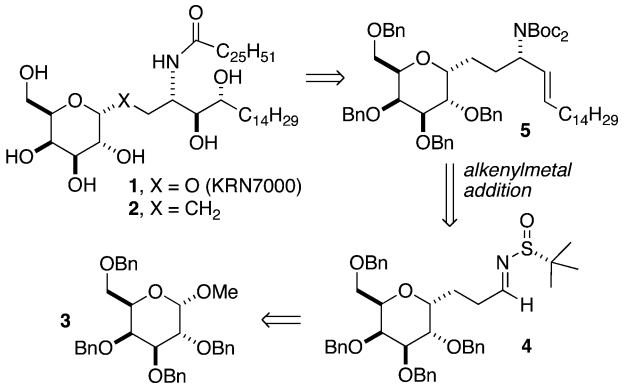
nitrogen in the glycoside side chain would provide molecules with interesting biological properties.[7] Accordingly, we envisioned *N-tert*-butanesulfinyl imine **4** as a key intermediate that could undergo a diastereoselective alkenylmetal addition followed by epoxidation and carbamate ring opening of **5** to generate compounds such as **2** in a rapid fashion (Scheme 1). From the outset, our requirements for this

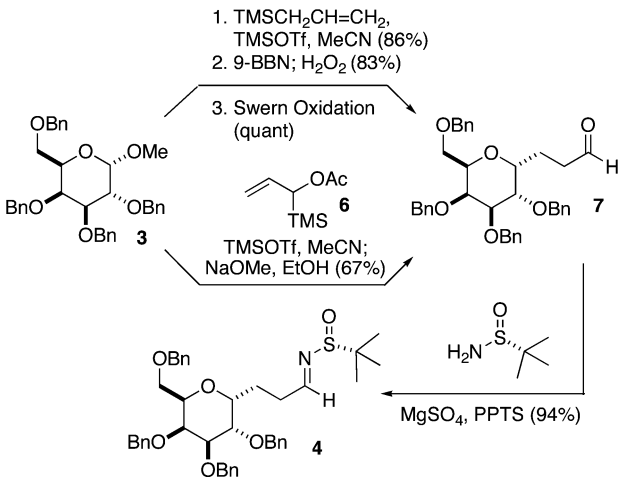
Scheme 1. Retrosynthetic Approach toward the α-*C*-Glycoside Analogue of KRN7000 (**2**)



undertaking were to synthesize **2** in the shortest possible sequence and in a modular and stereoselective fashion.

Synthesis of aldehyde **7** was readily accomplished using a literature procedure[7] that entailed allylation of **3** with allyltrimethylsilane, hydroboration/oxidation, and Swern oxidation to generate the desired aldehyde in 71% overall yield (Scheme 2). Later, we found that conditions developed

Scheme 2. Synthesis of Imine **4** via Allyltrimethylsilane Addition

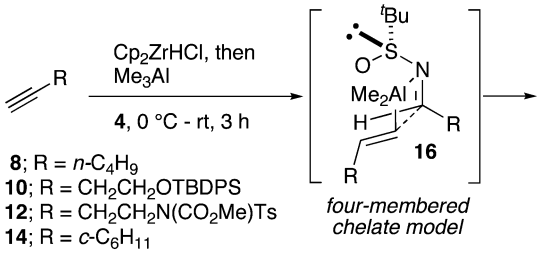


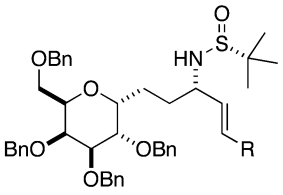
by Panek[8] employing acetyloxyallylsilane **6** as a homoenolate equivalent could be used to convert **3** via the resulting enol acetate[9] in situ to the desired aldehyde **7** in 67% yield (Scheme 2). All attempts to employ silyloxyallylsilanes in this transformation failed, however. Conversion of aldehyde **7** to *N-tert*-butanesulfinylimine **4** was achieved in 94% yield.[10]

With an efficient synthesis of imine **4** established, we directed our efforts toward the stereoselective alkenylmetal addition. Initial studies focused on the hydrozirconation[11] of alkynes followed by transmetalation to dimethylzinc which has proved effective for 1,2-addition to diphenylphosphinoylimines.[12] Unfortunately, a variety of solvents, temperatures, and external Lewis acids failed to promote this reaction.

Inspired by previous work in our group on the carboalumination−sulfinimine addition of alkynes,[13] we also investigated an alternative transmetalation of alkenyl zirconocenes to trimethylaluminum[14,15] and subsequent addition to **4**. To our delight, hydrozirconation of 1-hexyne (**8**) in CH_2Cl_2 at room temperature, addition of Me_3Al[16] followed by **4** at 0 °C, and subsequent warming to room temperature for 3 h generated the desired allylic amine **9** in 82% yield as a single diastereomer by ^1H NMR analysis (entry 1, Table 1).

Table 1. Hydrozirconation of Alkynes Followed by Transmetalation to Trimethylaluminum and Addition to *N-tert*-Butanesulfinylimine **4**





9; R = *n*-C_4H_9
11; R = $CH_2CH_2OTBDPS$
13; R = $CH_2CH_2N(CO_2Me)Ts$
15; R = *c*-C_6H_{11}

entry	alkyne	product	yield [%]
1	**8**	**9**	82[a]
2	**10**	**11**	81[a]
3	**12**	**13**	65[b]
4	**14**	**15**	85[a]

[a] Products were diastereomerically pure according to ^1H NMR analysis of the crude reaction mixtures. [b] A 93:7 mixture of diastereomers based on HPLC analysis; all yields are based on isolated, pure material.

Furthermore, we were able to demonstrate that silyl ether, carbamate, and sulfonamide functionalities were well toler-

(7) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; García, J. M.; González, A.; Odriozola, J. M.; Martin-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637 and cited references.

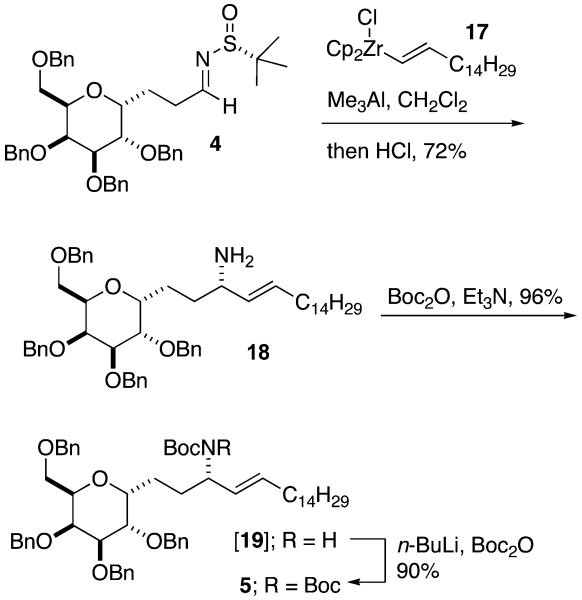
(8) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034. The reaction is also effective using conditions described in this report. A 67% yield was obtained on small scale; however, on larger scale, yields were variable.

(9) Formed as a 10:1 mixture of anomers and a mixture of (*E*/*Z*)-isomers.

ated and provided allylic amides in high yield and excellent diastereoselectivity (entries 2−4, Table 1). We propose the four-membered chelate model **16** to account for the observed selectivity, in analogy to additions of alkenylalanes derived from alkyne carboaluminations.[13] The mild and efficient conditions for generating *N*-*tert*-butanesulfinyl imines coupled with the rapid, stereoselective, and functional group tolerant method of alkenylalane addition described herein provide an attractive strategy for allylic amine synthesis.[17]

An extension of this method toward the synthesis of monoBoc-protected allylic amide **19** and bisBoc-protected allylic amide **5** was straightforward. Hydrozirconation of 1-hexadecyne to generate alkenylzirconocene **17**, followed by the aluminum transmetalation/imine addition and convenient in situ deprotection of the labile sulfinyl protecting group with aqueous HCl afforded the desired allylic amine in 72% yield (Scheme 3). A two step *N*-Boc-protection

Scheme 3. Alkenylalane Addition/Deprotection/Boc-Protection Sequence to Intermediate **5**

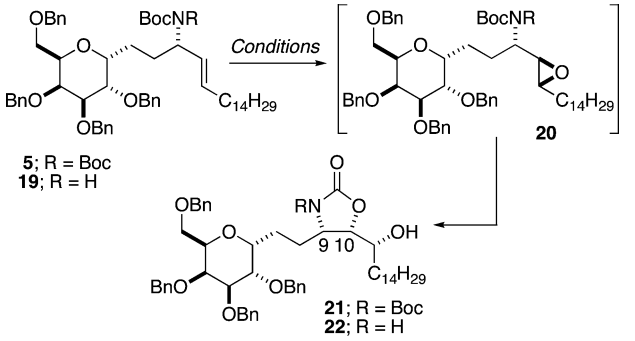


proved to be higher yielding than the one step approach. Our original strategy involved epoxidation of the allylic amide bearing the *tert*-butanesulfinyl protecting group; however, epoxidation of this species also oxidized the sulfur to generate the Bus protecting group[18] that could not be removed even under forcing conditions.

At this stage, conditions had to be identified to stereoselectively epoxidize the alkene **5** and effect the intramolecular cyclization of the *tert*-butylcarbamate to form oxazolidinone **21**.[19] Prior studies by Roush[20a] and O'Brien[20b] have demonstrated the feasibility of this sequence, although Roush employed trichloroacetamides and O'Brien focused on cyclic allylic amides.[20c]

Initial trials used MCPBA as the epoxidizing agent, under variable temperature and solvent conditions. The best result could be obtained at 0 °C in CH_2Cl_2 to yield 85% of **21** as a 1.6:1 mixture of diastereomers (entry 1, Table 2). In situ

Table 2. Evaluation of Oxidation Conditions to Generate Epoxide Intermediate **20** Followed by Intramolecular Opening of the Epoxide to Form Carbamate **21**



entry	substrate	conditions	yield [%], dr[a]
1	**5**	MCPBA, 0 °C	85, 1.6:1
2	**5**	oxone, $NaHCO_3$, acetone, rt	trace
3	**5**	TFAA, UHP, −20 °C, Na_2HPO_4	93, 9:1
4	**19**	TFAA, UHP, −20 °C, Na_2HPO_4	50, ND

[a]Yields refer to isolated, pure products. Diastereoselectivity was determined by HPLC analysis of the crude reaction mixtures.

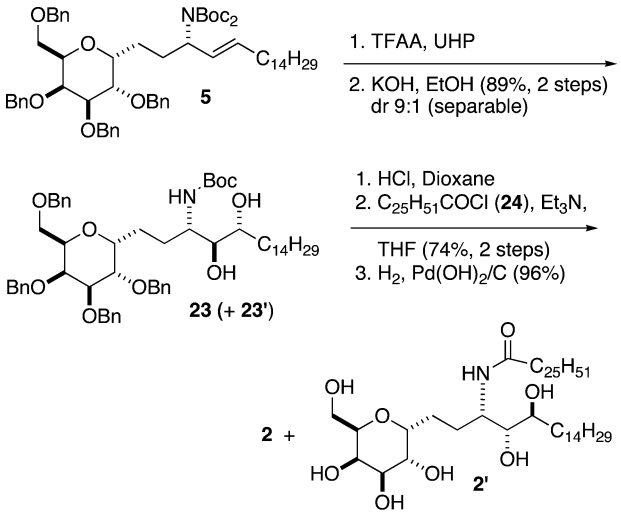
generated dimethyldioxirane (DMDO) was ineffective, producing no conversion after 20 h at room temperature. Increasing the electrophilicity of peracids has been shown to increase selectivity in directed epoxidations.[21] Trifluoroperacetic acid, generated in situ from trifluoroacetic acid

(10) For a review, see Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(11) For reviews, see (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2005**, *8*, 1.
(12) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (b) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.
(13) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.
(14) Although first demonstrated by Schwartz and Carr in 1977 with $AlCl_3$,[15] hydrozirconation/transmetalation to aluminum has not been explored further for addition to electrophiles.
(15) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638.
(16) The quality of Me_3Al is of critical importance in this reaction. Commercial solutions of Me_3Al were ineffective, possibly because of aggregate formation or traces of metal oxides; neat Me_3Al that was freshly diluted with CH_2Cl_2 was used in all cases.
(17) For a review, see Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
(18) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604.
(19) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558.
(20) (a) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127. (b) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955. (c) Although frequently observed as a side reaction, this sequence is rarely employed for *anti*-diol synthesis.
(21) (a) Jensen, A. J.; Luthman, K. *Tetrahedron Lett.* **1998**, *39*, 3213. (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2407. (c) Lee, K. W.; Hwang, S. Y.; Kim, C. R.; Nam, D. H.; Chang, J. H.; Choi, S. C.; Choi, B. S.; Choi, H.-W.; Lee, K. K.; So, B.; Cho, S. W.; Shin, H. *Org. Process Res. Dev.* **2003**, *7*, 839.

anhydride (TFAA) and urea-hydrogen peroxide (UHP) inclusion complex,[22] improved the selectivity of the epoxidation to 9:1 and increased the yield to 93% (entry 3, Table 2). MonoBoc protected amide **19** did not perform well in this reaction, seemingly because of an increase in decomposition. The assignment of the relative configuration in **20** was in accordance with previous reports;[20a] moreover, it was confirmed by coupling constant analysis[23] and by converting both diastereomers to the desired *C*-glycosides **2** and **2′**.[24]

Epoxidation of **5** under the TFAA/UHP conditions from entry 3 in Table 2 was accompanied by epoxide ring opening to give an *N*-Boc-protected carbamate (Scheme 4). Careful

Scheme 4. Completion of the Synthesis of the α-*C*-Galactosyl-ceramide Analogue of KRN7000[24]



reaction monitoring of a KOH/EtOH solution of this intermediate allowed the selective cleavage of the cyclic carbamate. *N*-Boc-protected amino diol **23** was thus obtained in 89% overall yield as a 9:1 mixture of diastereomers that were separated by column chromatography on SiO_2. Removal of the Boc group with HCl, coupling of the amine salt with acid chloride **24**[25] and global deprotection of the galactosyl benzyl ethers provided **2** in 71% yield over 3 steps.

(22) Taliansky, S. *Synlett* **2005**, 1962.

(23) Compound **21**: major isomer, $J_{9,10}$ = 9.5 Hz; minor isomer, $J_{9,10}$ = 5.2 Hz. These values are consistent with literature data wherein *cis*-oxazolidinones have larger coupling constants than *trans*-oxazolidinones: Bonini, B F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci. A.; Varchi, G. *J. Org. Chem.* **1999**, *64*, 8008.

(24) The 2 diastereomers of **23** (**23** and **23′**) were separated by column chromatography, and each diastereomer was carried separately through the remaining sequence with no notable differences. Yields for the sequence shown in Scheme 4 represent averaged values.

(25) Acyl chloride **24** was employed because of its greater solubility and ease of preparation compared to activated esters used previously: Heidelberg, T.; Martin, O. R. *J. Org. Chem.* **2004**, *69*, 2290.

Confirmation of the target structure was obtained by comparison of the $[\alpha]_D$ and ^{13}C NMR data of previously prepared **2**[4] with **2** and **2′**. As shown in Table 3, the ^{13}C

Table 3. Comparison of Representative ^{13}C NMR Chemical Shifts and $[\alpha]_D$ Values[a]

carbon no.[b]	Δ	δ 2'	δ 2 (lit.)	δ 2	Δ
12	-2.0	175.9	173.9	173.8	0.1
10	1.2	77.7	78.9	78.8	0.1
1	0.5	76.9	77.4	77.3	0.1
5	0.0	74.1	74.1	74.1	0.0
11	0.6	72.5	73.1	73.0	0.1
4	0.2	72.4	72.6	72.5	0.1
3	0.1	70.7	70.8	70.8	0.0
6	0.4	62.7	63.1	63.1	0.0
9	1.2	51.9	53.1	53.1	0.0
$[\alpha]_D$[c]	31.2	+9.6	+40.8	+38.4	2.4

[a] ^{13}C NMR data for **2** and **2′** were obtained in d_5-pyridine at 126 MHz. [b] Tentative assignments. [c] $[\alpha]_D$ values were obtained in pyridine (*c* 0.13) and are reported as average values of three measurements.

NMR data for **2** compare well with the literature data, while there are considerable differences with **2′**. Further support was achieved through comparison of $[\alpha]_D$ values.

In conclusion, we have developed a short (10 steps for the longest linear sequence, 12 overall transformations), stereoselective synthesis of the α-*C*-glycoside analogue **2** of KRN7000 (**1**). This process allows for analogue preparations at multiple points along the route. The synthetic sequence does not only showcase the utility of alkenylzirconocene-alkenylalane additions to *N*-*tert*-butanesulfinyl imines for the synthesis of enantiomerically pure allylic amines, but also the possibility to use a stereoselective *trans*-alkene epoxidation—intramolecular carbamate cyclization protocol as an attractive alternative to the dihydroxylation of *cis*-alkenes for the synthesis of *anti*-diols.

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Supporting Information Available: Experimental procedures and spectral data for **2**, **2′**, **4**, **5**, **7**, **9**, **11**, **13**, **15**, **18**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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