



## An improved method of ring closing metathesis in the presence of basic amines: application to the formal synthesis of (+)-lentiginosine and other piperidines and carbamino sugar analogs

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### ABSTRACT

A generalized method for performing ring closing metathesis in the presence of basic amines has been established and successfully used in the formal synthesis of (+)-lentiginosine as well as some valuable intermediates for the synthesis of several other azasugars and aminocyclitols.

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Metathesis

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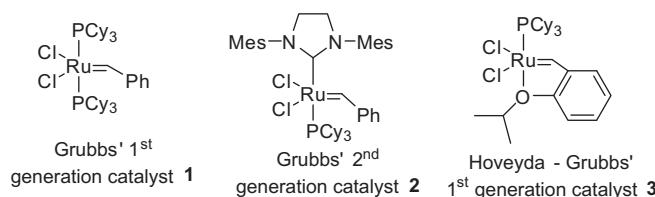
Lentiginosine

The ruthenium based catalyst **1** (bis(tricyclohexylphosphine)benzylidene ruthenium(IV) chloride, **Fig. 1**), first developed by Grubbs et al. for double bond exchange reactions, has witnessed enormous application in the synthesis of medium to large size carbacycles as well as heterocycles via a process popularly called as Ring Closing Metathesis (RCM).<sup>1</sup> Further improvement in the catalyst potency was brought about by changing the ligands around the metal center resulting in newer generation catalysts (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro (phenylmethylene)(tricyclohexylphosphine)ruthenium, **2** and dichloro(o-isopropoxyphenylmethylene)(tricyclohexylphosphine)-ruthenium (II), **3**.<sup>2</sup> The low oxophilicity, ease in handling and their ability to tolerate a number of functional groups have made these catalysts extremely useful in complex synthetic endeavours.<sup>3</sup> Very recently, Grubbs and co-workers<sup>4</sup> have reported that these ruthenium catalysts are effective even in concentrations as low as 500 ppm resulting in carbamate protected cyclic amines in excellent yields.

In the past decade, even though the use of ruthenium catalysts in the synthesis of azacycles has gained enormous importance<sup>5</sup> it has been well established that the presence of basic amines reduces the catalyst efficiency.<sup>6</sup> This is attributed to the fact that the lone pairs on nitrogen coordinate at the metal center making the latter unreactive toward the olefins.<sup>3,7</sup> Thus, amino groups have been conventionally converted into a carbamate, a sulfonamide, or an amide functionality before performing the RCM reac-

tions.<sup>5</sup> This often leads to an increase in protection–deprotection manipulation and in turn reduces the effectiveness of the synthetic sequence. Although, modifications of the reactant by using the corresponding ammonium salts,<sup>8</sup> or addition of protic<sup>9</sup> or Lewis<sup>10</sup> acids have been found useful, the viability of these approaches in the presence of acid sensitive groups is low. Recently, some sporadic reports of cyclization in presence of tertiary amines have emerged in the literature<sup>11</sup> that essentially requires 8–10 mol % catalyst loading, longer reaction times, and yields are moderate, especially for the six-membered rings. Considering the high cost of the commercial catalysts, such reaction conditions become impracticable in multi-step large scale synthesis.

Recently, synthesis of nitrogen containing sugar mimics has gained considerable importance<sup>12</sup> due to their therapeutic potential against viral infections, metabolic disorders, lysosomal storage disorders and cancer.<sup>13,14</sup> Among the azasugars, (+)-lentiginosine **24** (**Scheme 2**) is the least hydroxylated alkaloid, which was isolated from the leaves of *Astragalus lentiginosus* in 1990.<sup>15</sup> The



**Figure 1.** The most popularly used catalysts for olefin metathesis.

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molecule shows selective amyloglucosidase inhibition activity at submicromolar concentration ( $IC_{50} = 0.43 \mu\text{g}/\text{L}$ ) and is the most potent and selective amyloglucosidase inhibitor known till date. Due to the biological importance, several groups have reported its synthesis using either a chiral pool starting material or a chiral catalyst, which has often been achieved through long routes and intermediates formed in low yields.

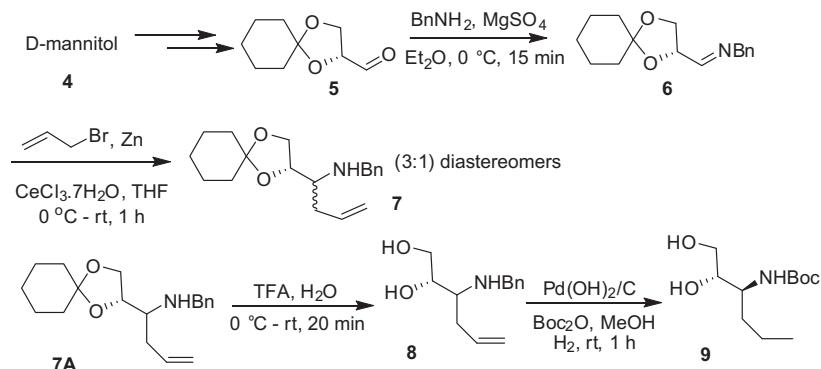
In continuation of our ongoing work in multistep syntheses en route to azasugars utilizing RCM as one of the key steps in C–C bond formation<sup>16</sup> we herein report the formal synthesis of (+)-lentiginosine and some advanced azasugar and aminocyclitol intermediates. Further, in contrast to the frequent observation made by us and others<sup>11,17</sup> that the presence of a basic amine in the reactant fails to provide high yield as compared to their conjugated counterparts, we have developed an improved procedure for olefin metathesis suitable to practice in the presence of tertiary amines, which has been used in the syntheses of sugar mimics.

In our present attempt to synthesize (+)-lentiginosine from D-mannitol **4** we are required to perform olefin metathesis in the early steps of the synthetic sequence, which demanded a good yielding reaction condition. The synthesis started from D-mannitol derived aldehyde **5**<sup>18</sup> (Scheme 1), which was converted to its corresponding imine **13** using  $\text{BnNH}_2$  in the presence of  $\text{MgSO}_4$  at  $0^\circ\text{C}$ . The Schiff base was formed in 15 min and was used without further purification. The Barbier reaction<sup>19</sup> on the imine derivative was done by reacting it with allyl bromide and zinc dust in presence of a catalytic amount of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  in dry THF. The reaction yielded a mixture of diastereomers **7** in 3:1 ratio, which was separated by column chromatography.

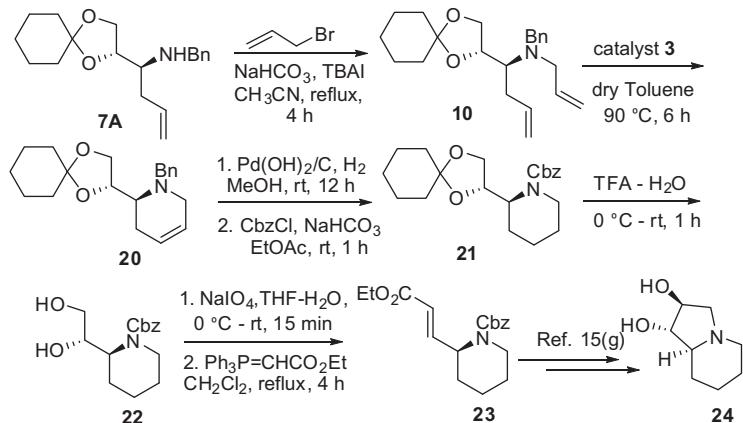
In order to establish the stereochemistry of the amine, the cyclohexylidene acetal group of the major isomer **7A** (Scheme 1) was deprotected and the so formed diol **8** was subjected to one pot N-debenzylation, olefin reduction and protection of the primary amine as its *t*-butyloxycarbamate using  $\text{Pd}(\text{OH})_2/\text{C}$  in  $\text{H}_2$  atmosphere. The product was obtained on purification as a white solid,  $\text{mp} = 89^\circ\text{C}$  (lit.<sup>20</sup> ref.  $\text{mp} = 90\text{--}91^\circ\text{C}$ ) and the absolute stereochemistry was confirmed to be as shown in diol **9**. Thus, the major isomer **7A** obtained from the Barbier reaction was suitable for the synthesis of (+)-lentiginosine.

N-Benzylated secondary amine **7A** was treated with allyl bromide and  $\text{NaHCO}_3$  in the presence of tetrabutylammonium bromide and was heated to reflux in  $\text{CH}_3\text{CN}$ . The diene **10** (Table 1) was obtained in 86% yield and its structure was confirmed by the presence of four terminal olefinic protons in the  $^1\text{H}$  NMR spectrum in the region  $\delta = 5.01\text{--}5.16$  and two internal olefinic protons in the region  $\delta = 5.70\text{--}6.02$ . This diene **10** was first subjected to olefin metathesis using Grubbs' 1st generation catalyst **1** (8 mol %) on a scale of 20 mg (0.059 mmol). The reaction occurred smoothly in refluxing dichloromethane and after 6 h the reactant was consumed completely and the cyclized product **20** (Scheme 2) was obtained in 69% yield.

An attempt of scaling up the reaction to 100 mg (0.293 mmol) of the diene resulted in utter disappointment. The reaction failed to progress more than 20% even on the increment of the catalyst amount to 15 mol %. Keeping in consideration that second generation catalysts are more reactive than the first generation we changed our reaction conditions. The diene **10** (0.293 mmol) was dissolved in 4 mL of dry toluene and 3 mol % of the catalyst **2**



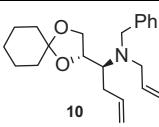
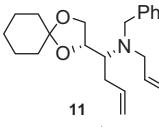
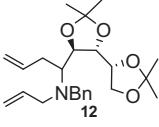
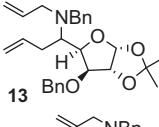
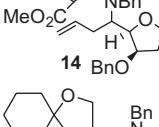
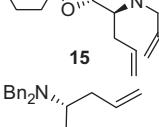
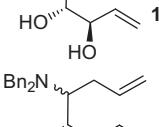
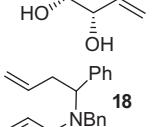
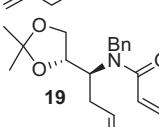
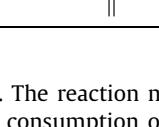
**Scheme 1.** Structure determination of the major diastereomer **7A**.



**Scheme 2.** Formal Synthesis of (+)-lentiginosine from **14A**.

**Table 1**

A comparison of RCM under single addition and portionwise addition of catalyst

S. No.	Reactant	Cat (mol %)	Single addition (%)	Addition in portions of three (%)	Time (h)
1		3	72	94	6
2		3	70	90	6
3		3	70	85	6
4		3	81	98	6
5		3	68	89	6
6		3	54	92	4
7		3	88	Quant.	2
8		3	79	95	2.5
9		2	72	86	5
10		3	86	Quant.	3

was added to it. The reaction mixture was heated to 90 °C. After 4 h, almost 50% consumption of the diene was observed by thin layer chromatographic (TLC) analysis. To our dissatisfaction the progress of the reaction stopped at this stage even on continuation of heating. On addition of another 3 mol % of the catalyst the reaction started to progress but came to a standstill after about 80% conversion. Completion of the reaction was brought about by further addition of 3 mol % of the catalyst and on purification, the product was obtained in 92% yield. To make the above described reaction cost effective with respect to Grubbs' catalyst, we wanted to minimize the amount of the catalyst required. Thus, we used 3 mol % of the catalyst **2**, which was divided in three equal portions and each portion was added to the reaction mixture at equal intervals in 6 h. The same reaction was also repeated using equal amount of the catalyst but added in a single portion. While the usual cyclization procedure yielded 72% of the product **20** with unreacted starting material being recovered, our modified reaction condition increased the yield to 94% with complete consumption of the starting material. We have been able to scale up the reaction to

500 mg (1.464 mmol) where the cyclization occurred smoothly. In order to generalize our newly developed reaction condition, we tested other dienes derived from sugar and non-sugar starting materials using 2–3 mol % Grubbs' 2nd generation catalyst. Our results are summarized in **Table 1**. While slow addition protocol has been employed to achieve RCM in very complicated systems,<sup>21</sup> we, hereby report the use of this tactic in the notoriously unreactive basic amine substrates for the first time.

In all cases a significant increase in yield was observed ranging from 12% to 38%. It is worth mentioning that cyclization of amine with deactivated nitrogen lone pairs **19** also underwent increase in yield by 14% when subjected to the modified conditions. The most striking increase was observed in **15** with a hike of 38% in yield. A plausible explanation for the improved yield of the reaction is the assumption that the active catalyst reacts with the available double bond faster than the nitrogen lone pairs. However, presence of high concentration of the basic amine in the reaction mixture in the form of either the diene or the cyclized olefin, eventually binds to the metal making it inactive. Adding small amounts of

the catalyst to the reaction mixture over a period of time ensures the presence of the active catalyst throughout the reaction time and reduces the possibility of binding with the basic nitrogen and thus increasing the yield of the cyclized product. This modified reaction procedure is expected to be useful in multistep synthesis as the sufficiently low catalyst loading enhances the utility of the reaction.

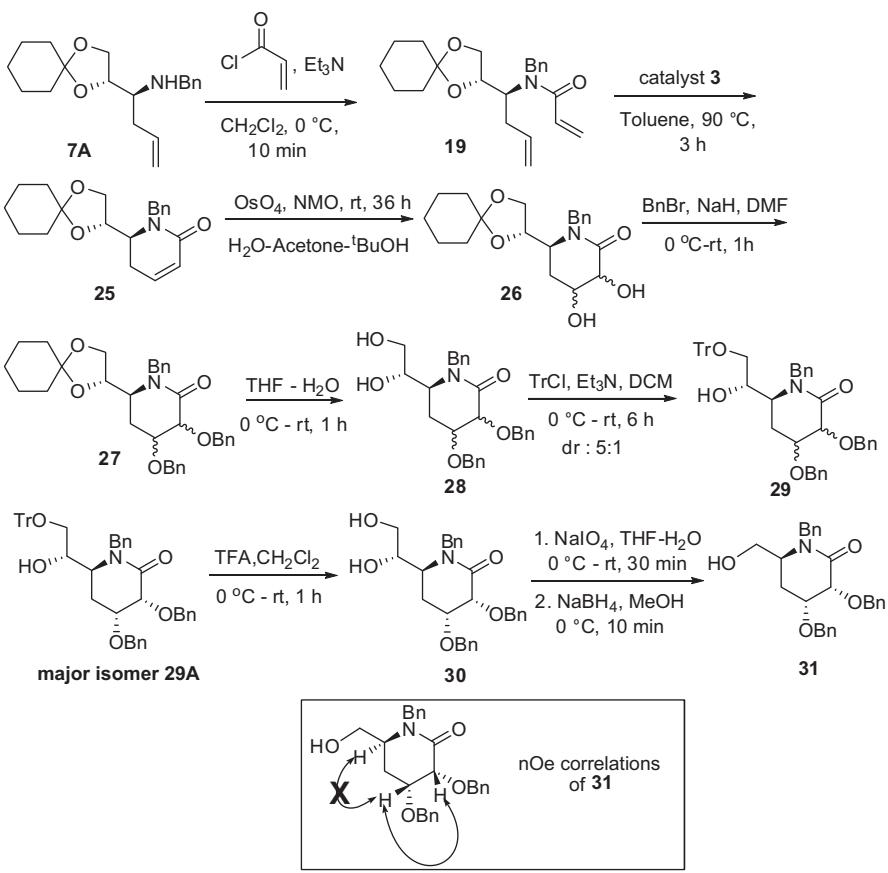
The synthesis of (+)-lentiginosine was continued (Scheme 2) by subjecting the cyclized product to one pot N-debenzylation and saturation of olefin using 20% w/w of  $\text{Pd}(\text{OH})_2/\text{C}$  in dry MeOH under  $\text{H}_2$  atmosphere. After 12 h the catalyst was removed by filtration over Celite® and the crude product was treated with benzyl chloroformate in 1:1 solution of ethyl acetate and saturated aqueous  $\text{NaHCO}_3$ . The corresponding *N*-carbamate **21** was obtained in 86% yield and its structure was confirmed by the presence of benzylic protons as a singlet at  $\delta$  5.13 equiv to 2 protons. Also, absence of olefinic peaks in  $\delta$  5.50–6.00 region suggested the successful reduction of the double bond. The cyclohexylidene acetal was hydrolyzed under acidic conditions to yield 1,2-diol **22** in 78% yield, which was oxidatively cleaved followed by the Wittig reaction to give  $\alpha,\beta$ -unsaturated ester **23**. This ester can be converted to (+)-lentiginosine following a literature procedure.<sup>15g</sup>

Utilizing the chiral free amine we then proceeded to synthesize polyhydroxylated piperidinones (Scheme 3). The free amine **7A** was reacted with acryloyl chloride and the corresponding amide **19** was treated with the catalyst **2**. The cyclic amide **25** was treated with a catalytic amount of  $\text{OsO}_4$  in the presence of NMO for 36 h. A diastereomeric mixture of diol **26** was obtained in 86% yield, which was dibenzylated by using benzyl bromide and sodium hydride. The mixture of diastereomers **27** was subjected to acetal deprotection in acidic medium. At all these stages we were unable to separate the diastereomers. The primary hydroxyl group was protected

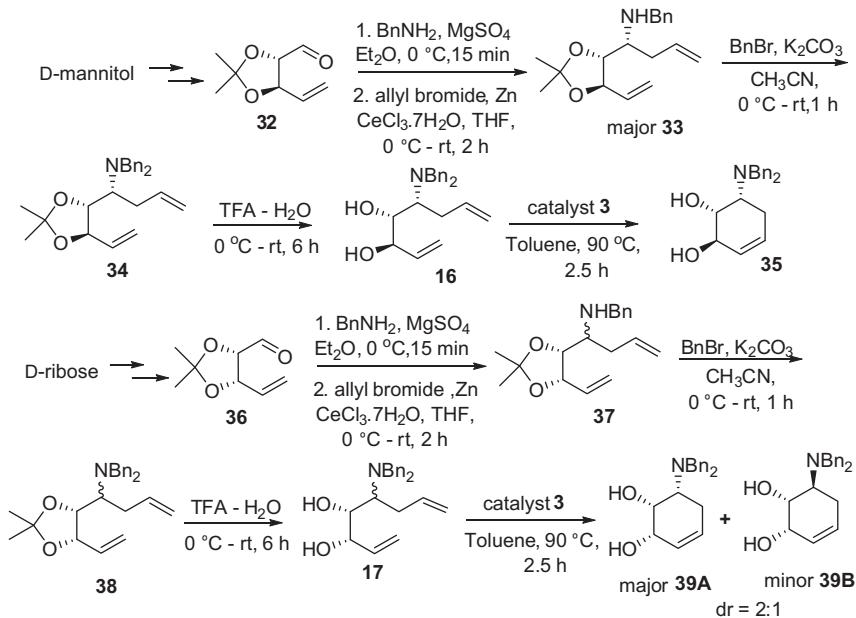
as its trityl ether **29** and column chromatographic purification of the product yielded the two diastereomers in 5:1 ratio. The major isomer **29A** was converted to the free diol **30** (Scheme 3) by removal of the ether protection with  $\text{CF}_3\text{CO}_2\text{H}$ . This molecule is an attractive intermediate for the synthesis of monocyclic azasugars. Also, cleavage of the diol into aldehyde and the corresponding reduction by using  $\text{NaBH}_4$  in MeOH gave a primary hydroxyl group containing piperidinone **31**. The absolute stereochemistry was determined by COSY and NOESY data of the compound **31** (see Supplementary data). Both the compounds viz. **30** and **31** could serve as useful intermediates toward the synthesis of azasugars.

The biological importance<sup>22</sup> of aminocyclitols, such as valienamine, valiolamine, voglibose, 2-deoxystreptamine, oseltamivir, and conduramines has attracted the attention of a number of chemists<sup>11c,23</sup> for their synthesis as well as that of their analogs. In view of this, the dienes **16** and **17**, derived from  $\text{D}$ -mannitol and  $\text{D}$ -ribose based aldehydes,<sup>24</sup> respectively, were prepared as shown in Scheme 4. In both the cases the cyclization in the presence of the acetonide protected 1,2-diol failed but the free hydroxylated compounds underwent RCM reactions successfully giving the corresponding substituted cyclohexenes in excellent yields. Although compound **33**, the major diastereomer, could be easily chromatographically purified at this stage, separation of the diastereomeric mixture of **37** was successful only after cyclization giving the two isomers viz. **39A** and **39B** in 2:1 ratio.

The absolute stereochemistry of compounds **35**, **39A**, and **39B** was determined by NOE correlation studies (Fig. 2). Thus, irradiation of H-2 in **39A** resulted in enhancement of H-6 proton by 3%. On the other hand, in **35** and **39B** no enhancement of H-6 proton was observed on irradiation of H-2. Thus, the stereochemistry was confirmed to be as shown in Figure 2. The N,N-dibenzylated aminocyclitols are suitable substrates for the synthesis of



Scheme 3. Synthesis of polyhydroxylated lactams.



Scheme 4. Synthesis of aminocyclitols.

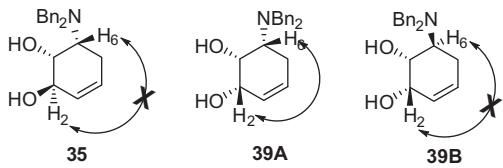


Figure 2. NOE correlations of aminocyclitols.

deoxystreptamine, conduramines, and deoxynosamines via simple organic transformations.<sup>17</sup>

In conclusion, we have developed a simple variation of the ring closing metathesis procedure to achieve excellent yields with low catalyst loading in the presence of nucleophilic amines. We have used this approach in the formal synthesis of (+)-lentiginosine, some piperidinones and carbamino sugar derivatives. Further utilization of this method and conversion of the azacycles into biologically important molecules are currently under progress in our laboratory.

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## Supplementary data

Supplementary data (experimental details, spectral data, and spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.020.

## References and notes

- (a) Grubbs, R. H. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, A31, 1829–1833; (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9856–9857.
- (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953–956; (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, 40, 2247–2250; (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, 122, 8168–8179; (d) Gessler, S.; Rndl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, 41, 9973–9976.
- Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, 115, 9858–9859.
- Kuhn, K. M.; Champagne, T. M.; Hong, S. H.; Wei, W. H.; Nickel, A.; Lee, C. W.; Virgil, S. C.; Grubbs, R. H.; Pederson, R. L. *Org. Lett.* **2010**, 12, 984–987.
- (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, 104, 2199–2238; (b) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, 63, 3919–3952.
- Compaan, P. *Adv. Synth. Catal.* **2007**, 349, 1829–1846.
- Grubbs, R. H. In *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; Vol. I.
- (a) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, 63, 9146–9147; (b) Rambaud, L.; Compaan, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, 12, 1807–1809; (c) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, 42, 3013–3015; (d) Liras, S.; Allen, M. P.; Blake, J. F. *Org. Lett.* **2001**, 3, 3483–3486; (e) Conn, S. J.; Blechert, S. *Bioorg. Med. Chem.* **2002**, 12, 1873–1876; (f) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, 5, 2323–2325; (g) Scheipe, B.; Glorius, F.; Leitner, A.; Fürstner, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 11960–11965; (h) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, 128, 3508–3509; (i) Déchamps, I.; Gomez-Pardo, D.; Cosy, J. *ARKIVOC* **2007**, 5, 38–45.
- (a) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, 2, 1847–1850; (b) Edwards, A. S.; Wybrow, R. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542–1544; (c) Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; Van der Marel, G. A.; Overkleeft, H.; van Boom, J. H. *J. Org. Chem.* **2003**, 68, 9598–9603; (d) Gracis, V.; Gasleki, A. F.; Moore, J. D.; Akritopoulou-Zanze, I.; Djuric, S. W. *Tetrahedron Lett.* **2006**, 47, 8977–8980; (e) Wijp, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, 124, 14848–14849; (f) Pearson, W. H.; Aponick, A.; Dietz, A. L. J. *Org. Chem.* **2006**, 71, 3533–3536; (g) Lee, J. H.; Shin, S.; Kang, J.; Lee, S. J. *Org. Chem.* **2007**, 72, 7443–7446.
- (a) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, 7, 871–874; (b) Abell, A. D.; Alexander, N. A.; Aitken, S. G.; Chen, H.; Coxon, J. M.; Jones, M. A.; McNabb, S. B.; Muscroft-Taylor, A. J. *Org. Chem.* **2009**, 74, 4354–4356.
- (a) Badorrey, R.; Catiuviela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Tetrahedron Lett.* **2004**, 45, 719–722; (b) Ayad, T.; Genisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, 3, 2626–2631; (c) Karanju, N. S.; Markad, S. D.; Dhavale, D. D. *J. Org. Chem.* **2006**, 71, 6273–6276; (d) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148; (e) Kim, S.; Lee, J.; Lee, T.; Park, H.-G.; Kim, D. *Org. Lett.* **2003**, 5, 2703–2706; (f) Pachamuthu, K.; Vankar, Y. D. *J. Organomet. Chem.* **2001**, 624, 359–363.
- (a) Stütz, A. *Inositols as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999; (b) Pearson, M. S. M.; Mathé-Alainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 31, 2159–2191; (c) Ferrier, R. J.; Blattner, R.; Clinch, K.; Furneaux, R. H.; Gardiner, J. M.; Tyler, P. C.; Wightman, R. H.; Williams, N. R. *Carbohydr. Chem.* **1996**, 28, 251; (d) Umezawa, W. *Adv. Carbohydr. Biochem.* **1974**, 30, 111–182.
- (a) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, 102, 515–554; (b) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, 38, 750–770.
- (a) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, 291, 2370–2376; (b) Chery, F.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *Tetrahedron* **2004**, 60, 6597–6608; (c) Alper, J. *Science* **2001**, 291, 2338–2343;

(d) Pavlovic, D.; Neville, D. C. A.; Argaud, O.; Blumberg, B.; Dwek, R. A.; Fischer, W. B.; Zitzmann, N. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 6104–6108; (e) Wu, S.-F.; Lee, C.-J.; Liao, C.-L.; Dwek, R. A.; Zitzmann, N.; Lin, Y.-L. *J. Virol.* **2002**, *76*, 3596–3604; (f) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539–2542; (g) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *3*, 561–574; (h) Cren, S.; Gurcha, S. S.; Blake, A. J.; Besra, G. S.; Thomas, N. R. *Org. Biomol. Chem.* **2004**, *2*, 2418–2420; (i) Paulsen, H.; Brockhausen, I. *Glycoconjugate J.* **2001**, *18*, 867–870; (j) Butters, T. D.; van den Broek, L. A. G. M.; Fleet, G. W. J.; Krull, T. M.; Wormald, M. R.; Dwek, R. A.; Platt, F. M. *Tetrahedron: Asymmetry* **2000**, *11*, 113–124; (k) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696.

15. (a) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1881–1886; (b) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630–4633; (c) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675–697; (d) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455–1456; (e) Shaikh, T. M.; Sudalai, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2287–2292; (f) Kim, I. S.; Li, Q. R.; Dong, G. R.; Kim, Y. C.; Hong, Y. J.; Lee, M.; Chi, K.-W.; Oh, J. S.; Jung, Y. H. *Eur. J. Org. Chem.* **2010**, *8*, 1569–1573; (g) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, M. V. *Tetrahedron Lett.* **1994**, *35*, 8871–8872.

16. (a) Pal, A. P. J.; Gupta, P.; Reddy, Y. S. *Eur. J. Org. Chem.* doi:10.1002/ejoc.201001102.; (b) Kumar, N.; Vankar, Y. D. *Org. Biomol. Chem.* **2009**, *7*, 2104–2109; (c) Dodd, V. R.; Kumar, A.; Vankar, Y. D. *Tetrahedron* **2008**, *64*, 9117–9122; (d) Kumar, A.; Rawal, G. K.; Vankar, Y. D. *Tetrahedron* **2008**, *64*, 2379–2390; (e) Dodd, V. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2007**, *33*, 5583–5589; (f) Reddy, B. G.; Vankar, Y. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2001–2004.

17. (a) Laventine, D. L.; Cullis, P. M.; García, M. D.; Jenkins, P. R. *Tetrahedron Lett.* **2009**, *60*, 3657–3660; (b) Laventine, D. M.; Jenkins, P. R.; Cullis, P. M. *Tetrahedron Lett.* **2005**, *56*, 2295–2298.

18. Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585–587.

19. Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766–7773.

20. (a) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Díez, R.; Gálvez, J. A. *Eur. J. Org. Chem.* **2002**, *22*, 3763–3767; (b) Iwama, S.; Segawa, M.; Fujii, S.; Ikeda, K.; Katsumura, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3495–3498.

21. (a) Gennari, C.; Castoldi, D.; Sharon, O. *Pure Appl. Chem.* **2007**, *79*, 173–180; (b) Skaanderup, P. R.; Jensen, T. *Org. Lett.* **2008**, *10*, 2821–2824; (c) Marvin, C. C.; Voight, E. A.; Suh, J. M.; Paradise, C. L.; Burke, S. D. *J. Org. Chem.* **2008**, *73*, 8452–8457; (d) Sukkari, H. E.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043–4046; (e) Gaich, T.; Mulzer, J. *Org. Lett.* **2005**, *7*, 1311–1313.

22. (a) Junge, B.; Heiker, F.-R.; Kurtz, J.; Müller, L.; Schmidt, R. R.; Wünsche, C. *Carbohydr. Res.* **1984**, *128*, 235–268; (b) Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K. *J. Antibiot.* **1984**, *37*, 1301–1304; (c) Kameda, Y.; Asano, N.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.* **1985**, *38*, 1816–1818; (d) Yasuda, K.; Shimowada, K.; Uno, M.; Odaka, H.; Adachi, T.; Shihara, N.; Suzuki, N.; Tamon, A.; Nagashima, K.; Hosokawa, M.; Tsuda, K.; Seino, Y. *Diabetes Res. Clin. Pract.* **2003**, *59*, 113–122; (e) Schmidt, A. C. *Drugs* **2004**, *64*, 2031–6046; (f) Russell, R. J.; Haire, L. F.; Stevens, D. J.; Collins, P. J.; Lin, Y. P.; Blackburn, G. M.; Hay, A. J.; Gamblin, S. J.; Skehel, J. J. *Nature (London)* **2006**, *443*, 45–49; (g) Lysek, R.; Vogel, P. *Tetrahedron* **2006**, *62*, 2768.

23. (a) Alegret, C.; Benet-Buchholz, J.; Riera, A. *Org. Lett.* **2006**, *8*, 3069–3072; (b) Murruzu, C.; Riera, A. *Tetrahedron: Asymmetry* **2007**, *18*, 149–154; (c) Chandrasekhar, B.; Madhan, A.; Rao, B. V. *Tetrahedron* **2007**, *63*, 8746–8751; (d) Nomura, H.; Richards, C. J. *Org. Lett.* **2009**, *11*, 2892–2895; (e) Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139–3143; (f) Machan, T.; Davis, A. S.; Liawruangrath, B.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 2725–2732; (g) Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552–6555; (h) Ayad, T.; Génisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626–2631; (i) Kaliappan, K. P.; Das, P.; Chavan, S. T.; Sabharwal, S. G. *J. Org. Chem.* **2009**, *74*, 6266–6274.

24. (a) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471–2479; (b) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. *Org. Lett.* **2005**, *7*, 5075–5078.