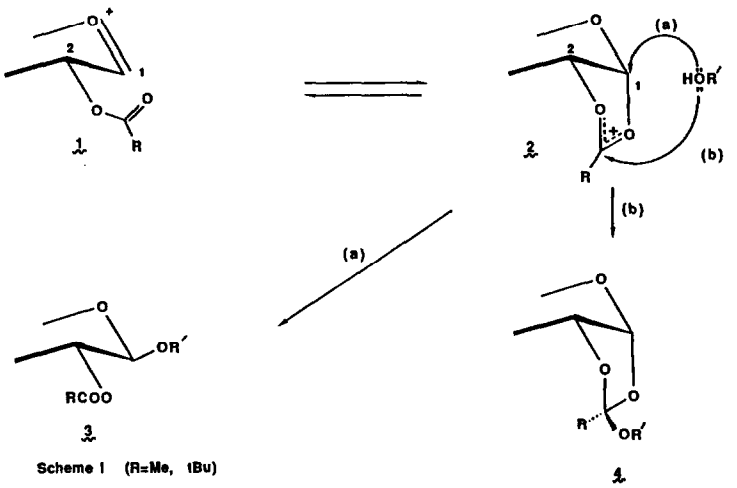
Tetrahedron Letters,Vol.29,No.33,pp 4097-4100,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN EFFICIENT APPROACH TO STEREOSELECTIVE GLYCOSYLATION OF CERAMIDE DERIVATIVES: USE OF PIVALOYL GROUP AS A STEREOCONTROLLING AUXILIARY[1)]

Susumu Sato, Shigeki Nunomura, Takahisa Nakano, Yukishige Ito,
and Tomoya Ogawa*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama, 351-01 Japan

Abstract: A remarkable effect of pivaloyl group as a stereocontrolling auxiliary at O-2a of glycosyl donors was demonstrated in order to improve the poor yield so far observed for the coupling between glycosyl donors and protected ceramides.

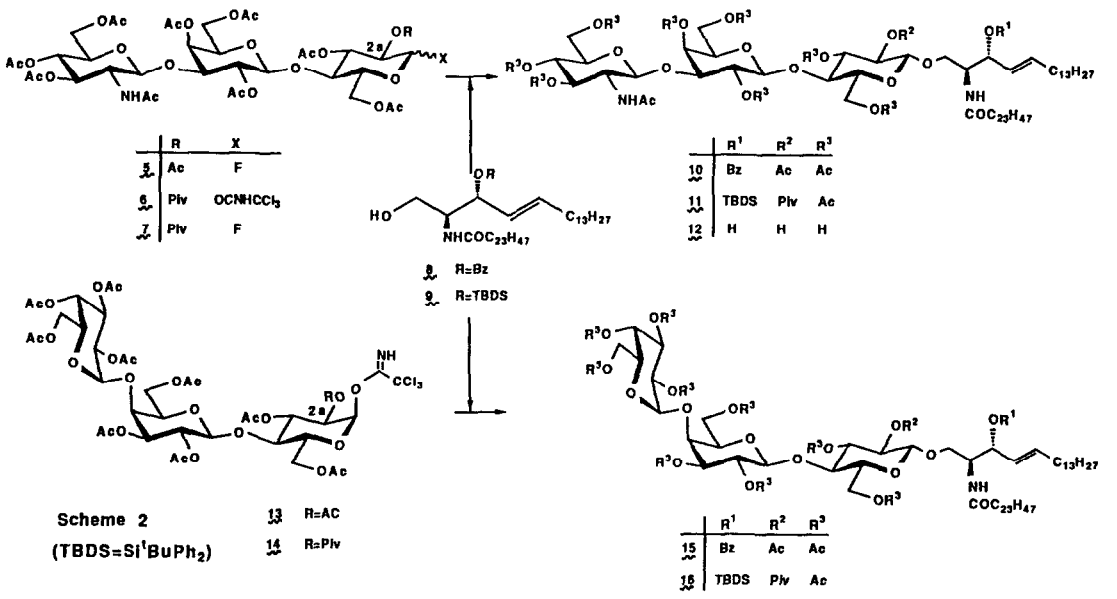
An oxocarbenium ion **1**, derived from a glycosyl donor with O-2 acyl group, gives rise to a more stable dioxocarbenium ion **2**[2)], which upon reaction with an alcohol R'OH affords either a 1,2-trans glycoside **3** or an orthoester **4** (scheme 1).



Scheme I (R=Me, tBu)

During the course of our experiments[3)] directed toward total synthesis of glycosphingolipids, it was demonstrated that coupling between peracetylated glycosyl donors and ceramide derivatives (**8** and **9**) gave particularly poor yields if glycan chains contain more than three monosaccharide residues. For example, the reaction of glycosyl donors **5** and **13** with **8** gave only trace (less than 5%)[4)] and 13% yield[5)] of the desired **10** and **15**, respectively. As the poor yields may result from the concomitant formation of an orthoester, use of pivaloyl instead of acetyl in **2** should disfavor[6)] the orthoester route (b) due to the presence of bulky t-butyl group next to the electrophilic carbon atom and eventually enhance the coupling efficiency along route (a).

To test this reasoning, glycotriaosyl donors **6**[7)], **7**[7)], and **14**[7)] that carry a stereocontrolling auxiliary at O-2a were prepared (*vide infra*). Crucial experiments were then performed. Trimethylsilyltriflate (TMSOTf) promoted glycosylation of **9** with imidates[8)] **6** and **14** did afford the desired **11**[7)] and **16**[7)] in 66 and 37% yield, respectively. Similarly, glycosylfluoride **7**, a 5:1 mixture of β and α anomers, was employed under the standard condition[9)] ($SnCl_2$, $AgOSO_2CF_3$) for

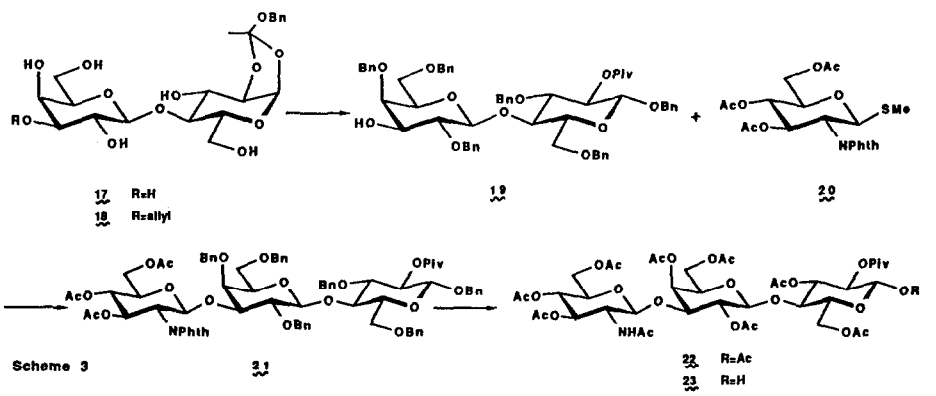


Scheme 2 (TBDS=Si^{t}BuPh$_2$)

the glycosylation of **9** to give **11** in 77% yield. Conventional deprotection of **11** (1. Bu_4NF in 1:1 THF-MeOH, 2. NaOMe-MeOH, 71% overall) afforded lacto-N-triaosylceramide **12**[10]. These results clearly revealed a remarkable stereocontrolling capability of pivaloyl auxiliary at O-2a in **6**, **7** and **14** which were prepared in a regiocontrolled way as follows.

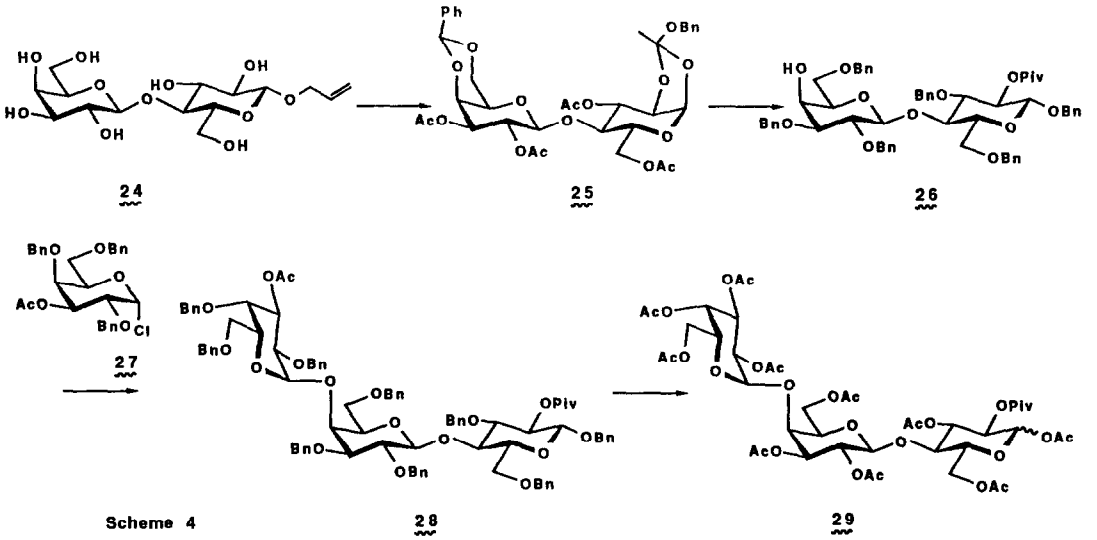
The orthoester **17** readily obtainable from peracetylated lactosylbromide was alkylated into monoallyl derivative **18**[7] in 96% yield (1. Bu_2SnO in 1:1 toluene-THF[11], 2. CH_2=$CHCH_2Br$, Bu_4NBr in THF). Conversion of **18** into **19**[7] was achieved in 5 steps (1. BnBr, NaH in DMF, 2. TMSOTf[12], 3. NaOMe-MeOH, 4. tBuCOCl, 5. $PdCl_2$-NaOAc-aq.AcOH[13], 65% overall). $CuBr_2$-Bu_4NBr-AgOTf promoted glycosylation[14] of **19** with thioglycoside **20** gave an 86% yield of **21**[7], which was then converted in 4 steps into **22**[7] as a 1:1 mixture of α and β anomers (1. NH_2NH_2•H_2O in EtOH, 2. Ac_2O-Py-DMAP, 3. Pd-C, H_2, 4. Ac_2O-Py-DMAP, 83% overall). Selective removal of O-1a acetyl group of **22** with NH_2NH_2•AcOH in DMF[15] gave a quantitative yield of **23**[7], which was further treated either with Cl_3CCN-DBU in $(ClCH_2)_2$ to give an 83% yield of **6** or with DAST in THF-$(ClCH_2)_2$ to give a 73% yield of **7** as a 5:1 mixture of β and α anomers.

Globotriaosyl donor **14** was prepared as follows. Conversion of allyl glycoside **24** into orthoester **25**[7] was performed in 5 steps (1. $PhCH(OMe)_2$, TsOH, 2. Ac_2O-Py-DMAP, 3. $PdCl_2$-NaOA-



Scheme 3

aq.AcOH, 4. CBr_4-$P(NMe_2)_3$ in THF, 5. BnOH-Bu_4NBr-Et_3N in CH_2Cl_2, 40% overall). **25** was further transformed into benzyl glycoside **26**[7] in 58% overall yield in 6 steps (1. NaOMe-MeOH, 2. BnBr-NaH in DMF, 3. TMSOTf in $(ClCH_2)_2$, 4. NaOMe-MeOH, 5. tBuCOCl, 6. BH_3•NMe_3-$AlCl_3$ in THF[16]). AgOTf promoted glycosylation of **26** with chloride **27**[17] in $(ClCH_2)_2$ at -20° afforded a 78% yield of **28**[7] which was then converted into a 1:1 mixture of α and β anomers **29**[7] (1. Pd-C, H_2, 2. Ac_2O-Py-DMAP, 77% overall). Treatment of **29** as in the case of **23** finally gave the desired imidate **14** in 52% overall yield.



Scheme 4

In conclusion, by employing pivaloyl group as a stereocontrolling auxiliary, efficiency of the glycosylation of ceramide derivatives became notably enhanced. Regioselective synthesis routes for the introduction of a pivaloyl auxiliary at O-2a were also established.

Acknowledgments. This work was partly supported by Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the NMR spectra and Dr. H. Yamazaki and his staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

Reference and Notes

1) Part 57 in the series "Synthetic Studies on Cell Surface Glycans". For part 56, see H. Iijima, M. Numata, M. Sugimoto, and T. Ogawa, submitted for publication.

2) K. Igarashi, *Adv. Carbohydr. Chem. Biochem.*, **34**, 243 (1977); H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, **21**, 155 (1982).

3) M. Sugimoto and T. Ogawa, *Glycoconjugate J.* , **2**, 5 (1985); M. Sugimoto, T. Horisaki, and T. Ogawa, *ibid.*, **2**, 11 (1985); K. Koike, M. Sugimoto, Y. Nakahara, and T. Ogawa, *ibid.*, **2**, 105 (1985); Y. Ito, M. Sugimoto, S. Sato, and T. Ogawa, *Tetrahedron Lett.*, **27**, 4753 (1986); S. Sato, Y. Ito, and T. Ogawa, *Carbohydr. Res.*, **155**, C1 (1986); M. Sugimoto, M. Numata, K. Koike, Y. Nakahara, and T. Ogawa, *ibid.*, **156**, C1 (1986); K. Koike, M. Sugimoto, Y. Nakahara, and T.

Ogawa, *Carbohydr. Res.*, **162**, 237 (1987); K. Koike, M. Sugimoto, S. Sato, Y. Ito, Y. Nakahara, and T. Ogawa, *ibid.*, **163**, 189 (1987); M. Numata, M. Sugimoto, K. Koike, and T. Ogawa, *ibid.*, **163**, 209 (1987); K. Koike, M. Mori, Y. Ito, Y. Nakahara, and T. Ogawa, *Glycoconjugate J.*, **4**, 109 (1987).

4) Y. Ito, S. Sato, M. Mori, and T. Ogawa, *J. Carbohydr. Chem.*, in press.

5) K. Koike, M. Sugimoto, S. Sato, Y. Ito, Y. Nakahara, and T. Ogawa, *Carbohydr. Res.*, **163**, 189 (1987).

6) H. Kunz and A. Harreus, *Liebigs Ann. Chem.*, 41 (1982); J. Vlahov and G. Snatzke, *Liebigs Ann. Chem.* , 570 (1983); R. R. Schmidt and P. Zimmermann, *Angew. Chem. Int. Ed. Engl.*, **25**, 725 (1986).

7) **6**: $[\alpha]_D$ +58.9° (c 0.6, $CHCl_3$), $\delta_H(CDCl_3)$ 6.505 (d, 3.7 Hz, H-1a). **7**: $\delta_H(CDCl_3)$ 5.687 (dd, 0.17 H, 2.6 and 53.0 Hz, H-1aα) and 5.314 (dd, 0.87 H, 5.8 and 52.5 Hz, H-1aβ). **11**: $[\alpha]_D$ -3.7° (c 0.5, $CHCl_3$), $\delta_H(CDCl_3)$ 5.333 (d, 3.4 Hz, H-4b), 5.015 (d, 7.9 Hz, H-1c), 4.419 (d, 7.9 Hz, H-1b), 4.313 (d, 7.9 Hz, H-1a), 1.124 (s, pivaloyl Me), 0.995 (s, tBu). **12**: $[\alpha]_D$ 0° (c 0.05, MeOH); $\delta_H(DMSOd_6$, 40°) 5.544 (td, 7.0, 15.0 Hz, H-5cer), 5.357 (dd, 7.0, 15.2 Hz, H-4cer), 4.629 (d, 7.9 Hz, H-1c), 4.270 (d, 6.7 Hz, H-1b), 4.169 (d, 7.6 Hz, H-1a), 3.051 (t, 7.9 Hz, H-2a), 1.833 (s, $COCH_3$). **14** : $\delta_H(CDCl_3)$ 8.680 (s, C=NH), 6.507 (d, 3.7 Hz, H-1a). **16**: $[\alpha]_D$ +12.2° (c 1.1, $CHCl_3$), $\delta_H(CDCl_3)$ 5.588 (dd, 1.8, 4.0 Hz, H-4c), 4.991 (d, 3.7 Hz, H-1c), 4.481 (d, 7.8 Hz, H-1b), 4.434 (d, 7.8 Hz, H-1a), 1.132 (s, pivaloyl Me), 0.996 (s, tBu). . **18**: mp 147-149°; $[\alpha]_D$ +40.5° (c 0.6, MeOH); $\delta_C(CD_3OD)$ 106.2 (1b), 98.9 (1a), 22.4 (Me). **19**: $[\alpha]_D$ -20.9° (c 0.7, $CHCl_3$), $\delta_H(CDCl_3)$ 5.130 (dd, 7.9 and 9.5 Hz, H-2a); $\delta_C(CDCl_3)$ 102.7 (1b), 99.7 (1a). **21**: $[\alpha]_D$ -13.4° (c 0.7, $CHCl_3$), $\delta_C(CDCl_3)$ 102.5 (1b), 99.7 (1a), 99.5 (1c). **22**: $\delta_H(CDCl_3)$ 6.294 (d, 0.5 H, 3.7 Hz, H-1aα) and 5.701 (d, 0.5 H, 8.2 Hz, H-1aβ). **25**: $[\alpha]_D$ +31.2° (c 1.7, $CHCl_3$), $\delta_H(CDCl_3)$ 5.503 (s, CHPh), 1.797 (s, CMe). **26**: $[\alpha]_D$ -3.8° (c 1.1, $CHCl_3$), $\delta_H(CDCl_3)$ 5.130 (dd, 7.8, 9.4 Hz, H-2a), 4.462 (d, 8.1 Hz, H-1b), 4.405 (d, 7.8 Hz, H-1a); $\delta_C(CDCl_3)$ 102.5 (1b), 99.6 (1a). **28**: $[\alpha]_D$ +42.6° (c 1.0, $CHCl_3$), $\delta_H(CDCl_3)$ 5.281 (dd, 3.0, 10.7 Hz, H-3c), 5.097 (dd, 8.1, 9.5 Hz, H-2a), 5.048 (d, 3.7 Hz, H-1c); $\delta_C(CDCl_3)$ 103.1 (1b), 100.1 (1c), 99.8 (1a). **29**: $\delta_H(CDCl_3)$ 6.295 (d, 0.5 H, 4.0 Hz, H-1aα) and 5.723 (d, 0.5 H, 8.3 Hz, H-1aβ).

8) R. R. Schmidt, *Angew. Chem. Int. Et. Engl.*, **25**, 212 (1986).

9) T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, 431 (1981); T. Mukaiyama, Y. Hashimoto, and S. Shoda, *ibid.*, 935 (1983).

10) S. Ando, K. Kon, M. Isobe, Y. Nagai, and T. Yamakawa, *J. Biochem*, **79**, 625 (1976).

11) J. Alais, A. Maranduba and A. Veyrieres, *Tetrahedron Lett.*, **24**, 2383 (1983); A. Maranduba and A. Veyrieres, *Carbohydr. Res.*, **135**, 330 (1985).

12) T. Ogawa, K. Beppu, and S. Nakabayashi, *Carbohydr. Res.*, **93**, C6 (1981).

13) R. Bose and R. Scheffold, *Angew. Chem.*, **88**, 578 (1976); T. Ogawa and S. Nakabayashi, *Carbohydr. Res.*, **93**, C1 (1981).

14) S. Sato, M. Mori, Y. Ito, and T. Ogawa, *Carbohydr. Res.*, **155**, C6 (1986).

15) G. Excoffier, D. Gagnaire, and J.-P. Utille, *Carbohydr. Res.*, **39**, 368 (1975).

16) M. Ek, P. J. Garegg, H. Hultberg, and S. Oscarson, *J. Carbohydr. Chem.*, **2**, 305 (1983).

17) **27** was prepared in 5 steps from allyl 2,6-di-O-benzyl-β-D-galactopyranoside (1. $PhCH(OMe)_2$-TsOH in DMF, 2. BH_3•NMe_3-$AlCl_3$ in THF, 3. Ac_2O-DMAP in Py, 4. $(Ph_3P)_3RhCl$-DABCO, then $HgCl_2$-HgO in aq. Me_2CO, 5. $SOCl_2$-DMF in $(ClCH_2)_2$, 54% overall). $[\alpha]_D$ +102.2° (c 1.5, $CHCl_3$); $\delta_H(CDCl_3)$ 6.127 (d, 3.9 Hz, H-1), 5.285 (dd, 2.9, 10.3 Hz, H-3).

(Received in Japan 26 April 1988)