ORGANIC LETTERS

2013
Vol. 15, No. 9
2270–2273

# 2,2-Dimethyl-4-(4-methoxy-phenoxy) butanoate and 2,2-Dimethyl-4-azido Butanoate: Two New Pivaloate-ester-like Protecting Groups

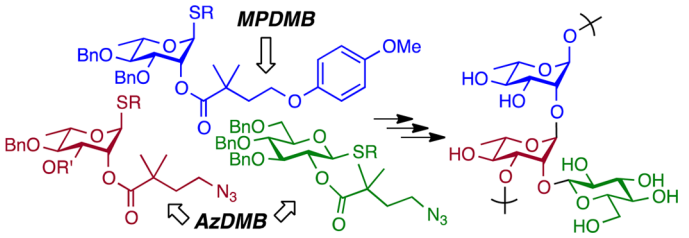
**Riccardo Castelli, Herman S. Overkleeft, Gijsbert A. van der Marel,* and Jeroen D. C. Codée***

*Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands*

*marel_g@chem.leidenuniv.nl; jcodee@chem.leidenuniv.nl*

**Received March 28, 2013**

## ABSTRACT




**The title compounds were developed to extend the available orthogonalities within the class of protecting groups removed by assisted cleavage. The mild, complementary (oxidative vs reductive) reaction conditions for the removal, together with their pivaloate-like character, were exploited, in combination with a levulinoyl-ester functioning as a third orthogonal protecting group, in the assembly of a *Streptococcus mutans* hexasaccharide built up from a oligorhamnose backbone featuring $\beta$-glucosyl appendages.**

The success of oligosaccharide synthesis heavily relies on the judicious choice of protecting groups to establish the correct connectivity, tuning the reactivity of the (mono)saccharide building blocks, and influencing the stereochemical outcome of the associated glycosylation reactions. The pivaloate stands among the ester-type hydroxyl protecting groups for its strong neighboring participation and ability to minimize the formation of orthoester byproducts, along with the tolerance of an ample range of reaction conditions.[1] This stability is paralleled by the forcing conditions required for its removal. To circumvent this drawback, the pivaloate moiety has been engineered by the connection through two methylene units of a masked primary alcohol, as reported by Crimmins,[2] Trost,[3] and Ensley.[4] Upon intramolecular lactonization (promoted by the Thorpe−Ingold effect of the *gem*-disubstitution) the unprotected hydroxyl group is released. While retaining the bulkiness adjacent to the carboxylate, the overall orthogonality and stability of the protecting group is translocated to the appending chain.[5]

To expand the orthogonalities of the aforementioned precedents and to establish two mutually orthogonal protecting groups, we considered making Kusumoto's 4-azidobutyryl ester a pivalate derivative,[6] thereby complementing the (2-azidomethyl)-benzoate ester reported by Sekine[7] and Seeberger.[8] In addition we used the *p*-methoxy

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: Hoboken, NJ, 1999. Pivaloyl orthoesters have been observed. See for example: (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2199. (b) Harreus, A.; Kunz, H. *Liebigs Ann. Chem.* **1986**, 717. (c) Codee, J. D. C.; Van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; Van Boom, J. H.; Van der Marel *Org. Lett.* **2003**, *5*, 1947.

(2) Crimmins, M. T.; Carroll, C. A.; Wells, A. J. *Tetrahedron Lett.* **1998**, *39*, 7005.

(3) Trost, B. M.; Hembre, E. J. *Tetrahedron Lett.* **1999**, *40*, 219.

(4) Yu, H.; Ensley, H. E. *Tetrahedron Lett.* **2003**, *44*, 9363.

(5) Crich, D.; Cai, F. *Org. Lett.* **2007**, *9*, 1613.

(6) Kusumoto, S.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1296.

(7) Wada, T.; Ohkubo, A.; Mochizuki, A.; Sekine, M. *Tetrahedron Lett.* **2001**, *42*, 1069.

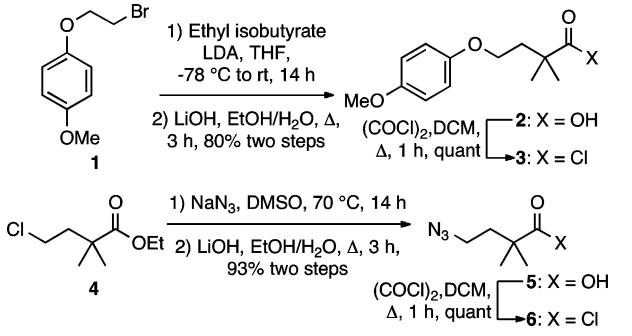
(8) Routenberg Love, K.; Andrade, R. B.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 8165.

10.1021/ol4008475 
**Published on Web 04/22/2013**

phenol-ether (PMP) as a masked nucleophile, because the oxidative conditions required to cleave the 4-methoxyphenol ether are well tolerated by azides and the reducing agents that transform an azide into the parent amine generally leave the PMP group unscathed.

The synthesis of the 2,2-dimethyl-4-(4-methoxy-phenoxy)-butanoate ester (MPDMB) precursors is straightforward. Alkylation of ethyl isobutyrate with bromide **1**,[9] followed by saponification, affords the crystalline acid **2** in good yield (Scheme 1). This compound is converted to the corresponding chloride **3** by treatment with a slight excess of oxalyl chloride in DCM at reflux, and reagent **3** can be used without purification.

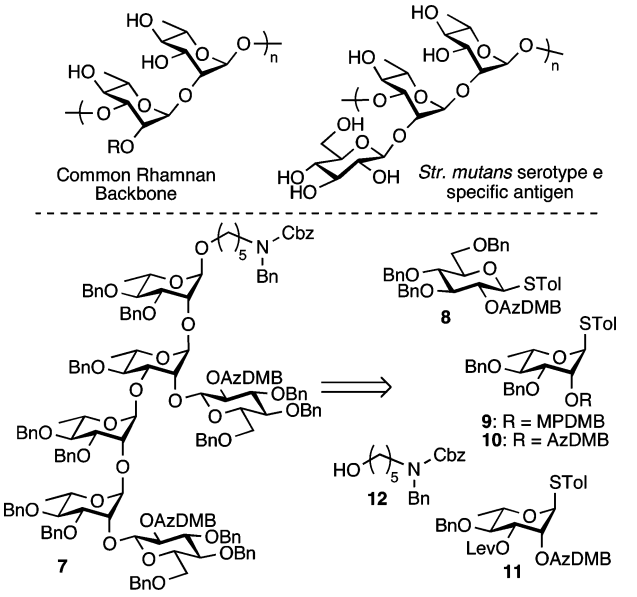
**Scheme 1.** Synthesis of the Protecting Group Precursors




The synthesis of the azido-functionalized counterpart (2,2-dimethyl-4-azido butanoate, AzDMB) is performed by reacting ethyl 2,2-dimethyl-4-chloro butanoate **4**[10] with sodium azide. Following saponification, the corresponding acyl chloride **6** was generated with an excess of oxalyl chloride in DCM at reflux, in analogy to acyl chloride **3**.

We decided to engage the obtained pivaloate derivatives in the assembly of an oligosaccharide, as the synthetic operations and protecting group manipulations involved represent an ideal setting to assess their properties. As an exemplary target, we identified the (polymeric) backbone of alternating (α1→2)- and (α1→3)-linked rhamnose units that constitute the group-specific polysaccharide antigens of Lancefield group A, C, and E streptococci, the serotype-specific antigen of *Streptococcus mutans* and *Streptococcus sobrinus* (Scheme 2).[11] The capsular polysaccharide of *S. mutans*[12] features additional glucose residues on this backbone located at the O2 of the (1→3)- linked rhamnose. In the case of *S. mutans*, serotype e the glucosyl appendages are *β*-linked. The generation of the pattern of alternating 1,2- and 1,3-*trans* rhamnosidic linkages in a linear fashion demands protection of the required building blocks with two distinct participating groups.[13] We envisaged accessing **7**, a dimeric form of the *S. mutans* type e trisaccharide repeating unit, employing MPDMB-functionalized building block **9** and AzDMB-functionalized **10** and **11**, the latter equipped with an *O*3-Levulinoyl ester to introduce the branching and complete the set of orthogonalities. With glucose building block **8** bearing an AzDMB group, *β*-linked branching could be introduced selectively in a multiple (2-fold) glycosylation fashion, and we projected cleavage of the AzDMB esters concomitantly with the benzyl-type protecting groups in the ultimate hydrogenolysis event. Target **7** could be equipped with a suitably protected amino-pentyl moiety **12** at the reducing end for potential further elaboration.

**Scheme 2.** Target Identification and Retrosynthesis




The preparation of the monosaccharide building blocks is depicted in Scheme 3. Thioglycosides **9** and **10** were obtained by reacting the sodium alkoxide of rhamnose thioglycoside **13**[14] with acyl chlorides **3** and **6**, respectively, in THF. The branching, central rhamnose unit **11** was obtained by first protecting the equatorial hydroxyl group of **14**,[14] by means of $Bu_2SnO$-mediated regioselective alkylation with PMBCl, followed by reaction of the axial hydroxyl with **6**, to furnish the AzDMB-ester. PMB-ether cleavage was performed under acidic conditions (with *p*-thiocresol as a cation scavenger)[15] and was followed by

(9) Schultz, D. M.; Prescher, J. A.; Kidd, S.; Marona-Lewicka, D.; Nichols, D. E.; Monte, A. *Bioorg. Med. Chem.* **2008**, *16*, 6242.

(10) Kuwahara, M.; Kawano, Y.; Kajino, M.; Ashida, Y.; Miyake, A. *Chem. Pharm. Bull.* **1997**, *45*, 1447.

(11) Shibata, Y.; Yamashita, Y.; Ozaki, K.; Yoshio Nakano, Y.; Koga, T. *Infect. Immun.* **2002**, *70*, 2891.

(12) Linzer, R.; Reddy, M. S.; Levin, M. J. In *Molecular microbiology and immunology of Streptococcus mutans*; Hamada, S., Michalek, S. M., Kiyono, H., Menaker, L., McGhee, J. R., Eds.; Elsevier Science Publishers: Amsterdam, The Netherlands, 1986; pp 29−38.

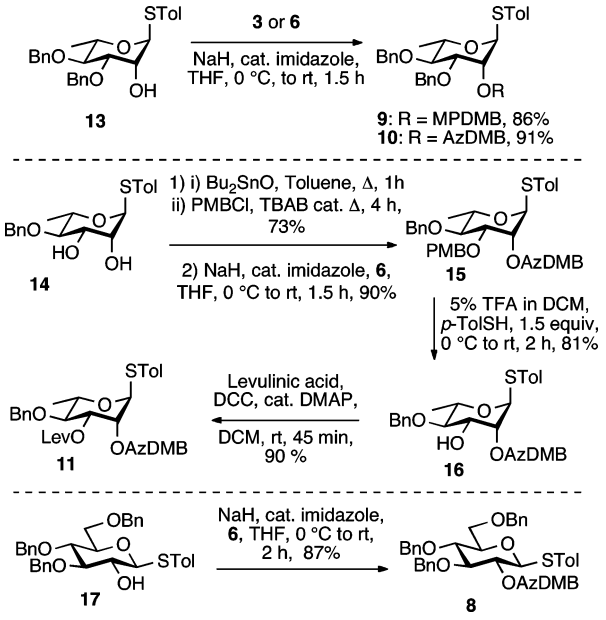
(13) For convergent approaches towards related structures, see: (a) Bedini, E.; Barone, G.; Unverzagt, C.; Parrilli, M. *Carbohydr. Res.* **2004**, *339*, 393. (b) Höög, C.; Rotondo, A.; Johnston, B. D.; Pinto, M. *Carbohydr. Res.* **2002**, *337*, 2023. (c) Mulard, L. A.; Clement, M.-J.; Imberty, A.; Delepierre, M. *Eur. J. Org. Chem.* **2002**, 2486.

(14) Rajput, V. K.; Mukhopadhyay, B. *J. Org. Chem.* **2008**, *73*, 6924.

(15) Using anisole as a scavenger led to isolation of the product in lower yield (48%), due to the expulsion of the *p*-thiocresyl moiety from the anomeric center. We excluded the use of DDQ. See: Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 3581.

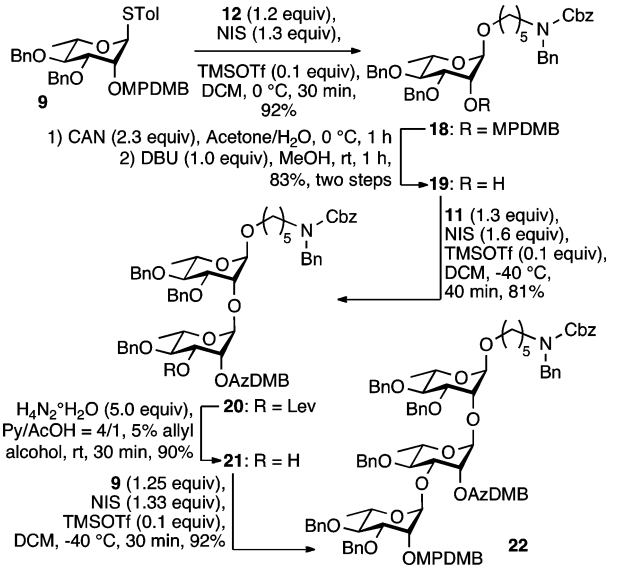
Steglich esterification with levulinic acid to produce **11**. Glucose building block **8** was accessed by reacting thioglucoside **17**[16] with sodium hydride and chloride **6**.

**Scheme 3.** Building Block Preparation




We commenced (Scheme 4) assembly of the target structure **7** by condensing **9** and **12** by exposure to NIS/TMSOTf in DCM.[17] The reaction occurred rapidly and in consistently high yield employing a slight excess of **12** at 0 °C. The absence of any byproduct deriving from potential electrophilic attack on the electron-rich 4-methoxyphenoxy moieties demonstrated the compatibility of the MPDMB with the glycosylation conditions employed.[18] We next investigated cleavage of the MPDMB group. To this end, cerium ammonium nitrate (CAN) was added in the form of an aqueous solution to a chilled solution of **18** in acetone. Twofold single-electron oxidation, followed by *ipso*-substitution by water, proceeded rapidly.[19] However, the unveiled primary alcohol did not spontaneously attack the carbonyl function of the ester to extrude the secondary alcohol and liberate the lactone. In line with the conditions reported by Ensley,[4] we exposed the crude[20] alcohol to a stoichiometric amount of DBU in methanol, to induce the hydroxyl group to cyclize and liberated product **19**.[21] The so-obtained acceptor was reacted with **11** at low temperature to give disaccharide **20**. Subsequent deprotection of the levulinoyl ester in **20** proceeded rapidly[22] without any detectable migration of the AzDMB group. After further rhamnosylation of **21** with **9**, trisaccharide **22** was obtained in excellent yield.

**Scheme 4.** Rhamnan Synthesis




At this stage we explored the key mutual orthogonality of the two protecting groups (Scheme 5). Treatment of an acetone solution of **22** with aqueous CAN was followed (after workup) by the addition of DBU in methanol. The two combined steps furnished compound **23** in 80% yield, demonstrating the compatibility of the AzDMB group with both oxidative and basic conditions employed. Cleavage of the AzDMB ester from **22** was performed by Staudinger reduction of the azide group with $PMe_3$ in THF/water. To drive the overall process of AzDMB deprotection to completion at an acceptable rate, it was found necessary to add a catalytic amount of aqueous KOH, to speed up the hydrolysis of the intermediate imino-phosphorane. The liberated primary amine uneventfully engaged in the intramolecular 2,2-dimethyl $\gamma$-butyrolactam formation to release the deprotected secondary alcohol.[23,24]

(16) Chayajarus, K.; Chambers, D. J.; Chughtai, M. J.; Fairbanks, A. J. *Org. Lett.* **2004**, *6*, 3797.

(17) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.

(18) (a) Panchadhayee, R.; Misra, A. K. *Tetrahedron: Asymmetry* **2010**, *21*, 2142. (b) Clausen, M. H.; Madsen, R. *Chem.—Eur. J.* **2003**, *9*, 3821. In a related experiment, we were able to selectively hydrolize the thioglycoside moiety of **9** with NBS in wet acetone. See Supporting Information.

(19) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(20) Washing with an aqueous, basic solution containing 2 equiv of cysteine during the workup, the generated 1,4-benzoquinone byproduct is converted into hydrophilic species, simplifying the chromatographic purification in the subsequent step. Crescenzi, O.; Prota, G.; Schultz, T.; Wolfram, L. J. *Tetrahedron* **1988**, *44*, 6447.

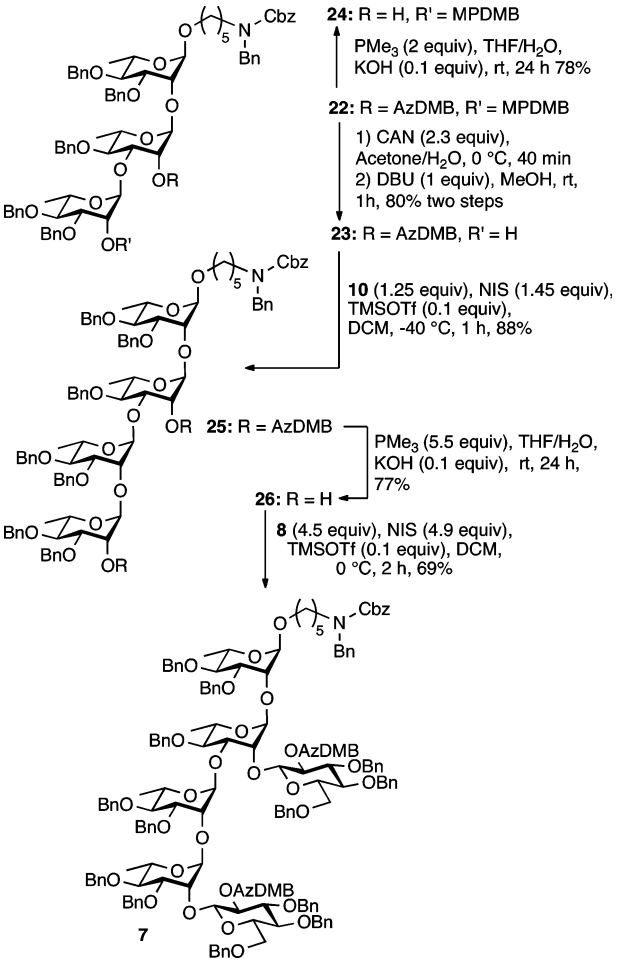
(21) The $R_f$ for the primary alcohol and the deprotected secondary alcohol are the same. Monitoring the reaction by $^1H$ NMR (0.03 M in $CD_3OD$) showed full conversion in less than 1 h.

(22) Hanashima, S.; Castagner, B.; Esposito, D.; Nokami, T.; Seeberger, P. H. *Org. Lett.* **2007**, *9*, 1777.

(23) More basic conditions employed during the Staudinger reduction of azide groups have also been reported: Arungundram, S.; Al-Mafraji, K.; Asong, J.; Leach, F. E., III; Amster, I. J.; Venot, A.; Turnbull, J. E.; Boons, G.-J. *J. Am. Chem. Soc.* **2009**, *131*, 17394.

(24) Cleavage of the AzDMB group could also be effected employing exc. $NaBH_4$/cat. $NiCl_2$ in EtOH. However these cleavage conditions gave varying poorly reproducible outcomes, which seemed to depend on the cosolvent ($Et_2O$ or ethyl acetate) used to solubilize the substrate. The reproducibility of the homogeneous $PMe_3$/cat. KOH system discouraged further investigations along this line.

**Scheme 5.** Selective Cleavage and Completion of the Synthesis




Continuing the synthesis from **23**, rhamnosylation with thioglycoside **10** furnished the bis-AzDMB protected tetrasaccharide **25**, from which both esters were selectively cleaved employing an excess of $PMe_3$ and a catalytic amount of KOH to give **26**. We finally took on the double glucosylation of tetrarhamnoside **26**.[25] With a modest excess of donor **8** (2.8 equiv) at 0 °C, hexasaccharide **7** was obtained in 55% yield. Lowering the temperature to −25 °C had a detrimental effect, while employing a larger excess (4.5 equiv) of **8** at 0 °C raised the yield of **7** to a more satisfactory 69%.

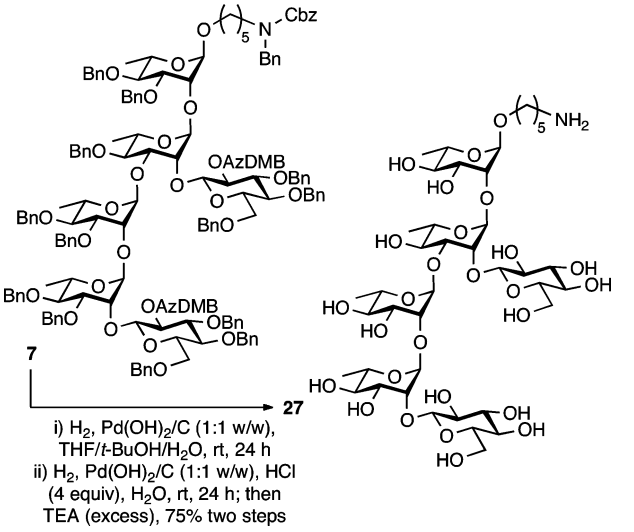
Final deprotection of **7** could be effected via a hydrogenolysis event, in which all the benzyl groups, the benzylcarbamate, and the AzDMB esters were removed (Scheme 6).

(25) To test the reactivity profile of **8** we set a scouting reaction with **19** as the model acceptor. Under the promotion of NIS/TMSOTf at 0 °C we obtained the corresponding disaccharide with complete $\beta$-selectivity in 85% yield. See Supporting Information for details.

The hydrogenolysis was effected in two stages. A first cycle of hydrogenolysis in a THF/*t*-BuOH/$H_2O$ solvent mixture reduced the Cbz-group and the two AzDMB esters to liberate the primary amine functions and some of the alcohol functions. The resulting partially deprotected material was redissolved in water, and 4 equiv of HCl were added to neutralize the generated primary amines, followed by a second hydrogenolysis round. After removal of the catalyst, the addition of an excess of triethylamine to the filtrate (to neutralize the acid, which is potentially harmful to rhamnosidic linkages) finally triggered the cyclization to 2,2- dimethyl-$\gamma$-butyrolactam, thereby furnishing the fully deprotected compound **27**.

In summary, we have developed two structurally related, pivaloate-like protecting groups that are cleaved under mild, mutually orthogonal reaction conditions that make them a self-contained orthogonal set. Complementary with a third temporary protecting group, we established their performances in the linear synthesis of a complex oligosaccharide sequence, representing two repeating units of the *S. mutans* type e antigen.

**Scheme 6.** Global Deprotection




**Acknowledgment.** This work was supported by The Netherlands Organization for Scientific Research (NWO).

**Supporting Information Available.** Experimental procedures and analytical data for all the new compounds are given in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.