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A New Acetal Resin Valuable for the Solid-Phase Synthesis of 1-Oxacephams *via* a Cyclization/Cleavage step

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Abstract: Synthesis of benzyloxybenzaldehyde dimethyl acetal resin **7** and its usefulness for immobilising 1,3-diols is described. The regioselective cleavage with DIBAL-H in CH_2Cl_2 of the resin-bound acetals **10** and **11** provided the polymer-bound alcohols **12** and **13** which were used as starting materials in the solid-phase synthesis of 1-dethia-1-oxacephams.

Keywords : azetidinones; solid-phase synthesis; resins; cyclization/cleavage

Solid-phase organic synthesis (SPOS) has attracted great attention over the past several years [1]. Combinatorial application of SPOS enables the preparation of large numbers of structurally related molecules in short periods of time, which is of great importance for the development and improvement of lead structures in the pharmaceutical and related industries. The increasing bacterial resistance against commonly used penicillins and cephalosporins is causing a continous search for new β-lactam antibiotics and β-lactamase inhibitors. Recently we have directed our attention to the development of new methodologies for the solid-phase synthesis of 1-dethia-1-oxacephams representing a class of compounds with potential biological value [2]. In spite of their importance, the solid-phase synthesis of β-lactams has been barely reported [3]. Very recently we have described a new methodology for the stereoselective solid-phase synthesis of 1-oxacephams [4]. This methodology is based on a new cyclization/cleavage step in which the formation of a six-membered ring proceeds with simultaneous cleavage of the final product from the resin. Only the target molecule undergoes the cyclization reaction and can be released. In the past, this strategy was mainly used for the synthesis of molecules having an amide function [5], for palladium-mediated metathesis [6] and the formation of macrocyclic lactones [7]. Our approach to 1-oxacephams uses 4-vinyloxyazetidin-2-one **1**, a β-lactam building block, recently introduced by one of us [8]. The

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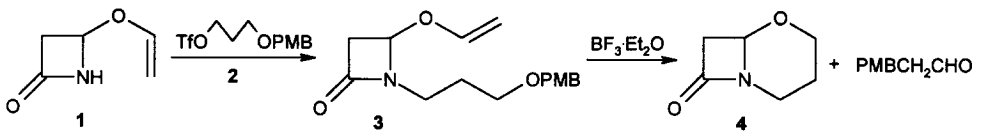
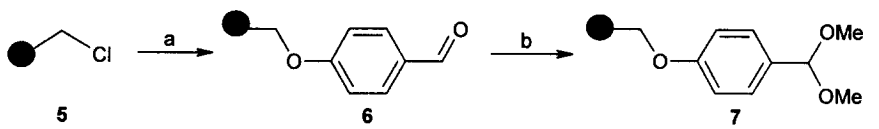
simplest example of this strategy, depicted in Scheme 1, consists of *N*-alkylation of **1** by a suitably prepared 1,3-propanediol derivative **2** prior to the cyclization step which involves the nucleophilic substitution at C-4 of the azetidin-2-one ring to afford **4** [8d].



Scheme 1

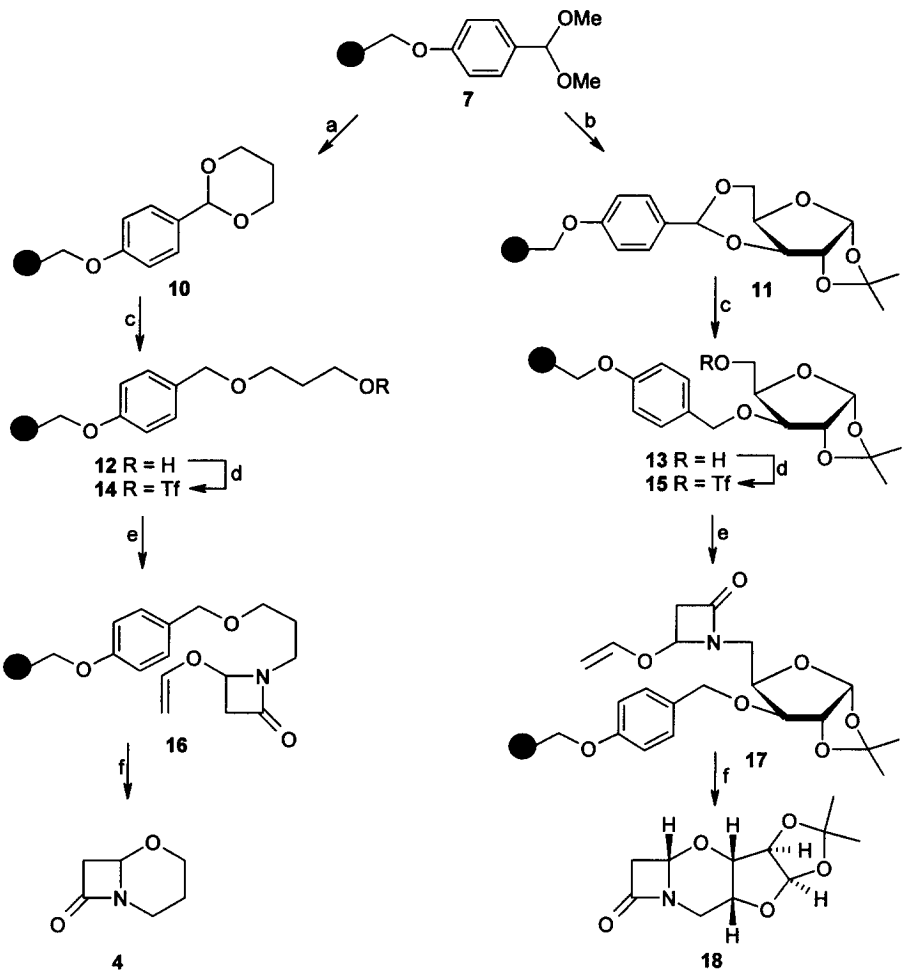
In the preliminary report we applied this strategy to the synthesis of 1-oxacephams on solid-phase. Wang trichloroacetimidate resin [9] was used as an immobilising reagent for chiral alcohols. The resin-bound alcohols were transformed into the *N*-alkylated polymer-bound 4-vinyloxyazetidin-2-one. In the cyclization/cleavage step, the 4-benzyloxybenzyl-type protection of the hydroxy group derived from the Wang resin activates the oxygen atom allowing efficient cyclization/cleavage from the resin while the 4-benzyloxybenzyl cation and the acetaldehyde anion are liberated. These encouraging results prompted us to further develop of our methodology. In this paper we report an efficient method for the synthesis of a new dimethylacetal resin **7**, useful for the formation of resin-bound cyclic acetals from 1,3-diols, and its application to the solid-phase synthesis of β-lactams. Other examples for the immobilisation of diols on polymer support have been described recently [10].



Scheme 2. *Reagents and conditions:* a) 4 eq. 4-hydroxybenzaldehyde 4 eq. NaH, DMF, 60 °C, 24 h; b) $HC(OMe)_3$, 0.1 eq. TsOH, 48 h, r.t.

Merrifield resin (1 mmol of Cl per gram of resin) **5** was reacted with the sodium salt of 4-hydroxybenzaldehyde in DMF to give the derivative **6** which was converted into the more reactive dimethylacetal resin **7** (Scheme 2). Attachment of the 1,3-diols to the resin **7** was achieved using pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane at room temperature. We used achiral 1,3-propanediol (**8**) and 1,2-*O*-isopropylidene-α-D-xylofuranose (**9**) as starting materials for the synthesis of 1-oxacephams (Scheme 3). The cyclic acetal **10** can be obtained from **7** upon treatment with an excess of **8** in the presence of PPTS in CH_2Cl_2. The coupling of **9** to the resin **7** proceeded in 80 % yield, calculated after recovery of the sugar from the polymer **11** with 10 % TFA/CH_2Cl_2 (30 min). The six-membered ring of the polymer-bound

acetals **10** and **11** can be opened by treatment with DIBAL-H (3 eq. DIBAL-H, CH_2Cl_2, -70 to -20 °C, 4 h).



Scheme 3. *Reagents and conditions:* a) 4 eq. 1,3-propanediol (**8**), 0.2 eq. pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2 20 °C, 24 h; b) 4 eq. 1,2-*O*-isopropylidene-α-D-xylofuranose (**9**), 0.2 eq. PPTS, CH_2Cl_2, 20 °C, 24 h; c) 3 eq. DIBAL-H, CH_2Cl_2, -70 → -20 °C 4 h; d) 5 eq. Tf_2O, 7 eq. 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h; e) 3 eq. **1**, 6 eq. *n*BuLi, 3 eq. Bu_4NHSO_4, THF, -70 → 20 °C, 12 h; f) 1 eq. $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C, 3 h.

In the case of **11**, ring opening is highly regioselective to provide the polymer-bound alcohol **13** in 70 % yield. Treatment of the resin-bound alcohols **12** and **13** with triflic anhydride and 2,6-lutidine in CH_2Cl_2 yielded the corresponding triflates **14** and **15**. *N*-Alkylation of **1** was accomplished after the deprotonation of **1** with a mixture of *n*-BuLi and Bu_4NHSO_4 (2:1) in THF at -70 °C followed by addition of the resin **14** or **15** to this solution. In each case the reaction took overnight. The progress of the alkylation can be monitored with IR, following the appearance of the characteristic absorption of the β-lactam carbonyl group

(1768cm^{-1} for **16** and 1774cm^{-1} for **17**). The 1-oxacephams **4** and **18** were obtained in 20 % yield over five steps by the cyclization/cleavage stage of **16** and **17** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 according to the procedure described before [4]. The cepham **18** was obtained in high diastereometric purity. The configuration of **18** was proved by comparision with previously reported data [8b,11]. Owing to the simplicity and high regioselectivity of the benzylidene acetal opening, the present methodology offers some advantages over the previously reported one which has been based on the protection-benzylation-deprotection sequence.

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References

[1] a) J. Früchtel, G. Jung, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17-42; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.*, **1996**, *96*, 555-600; c) P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron*, **1996**, *52*, 4527-4554; d) P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron*, **1997**, *53*, 5643-5678; e) S. Booth, P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron*, **1998**, *54*, 15385-15443.

[2] a) W. Nagata, *Pure Appl. Chem.* **1989**, *61*, 325-336; b) S. Shibahara, T. Okonogi, Y. Murai, T. Kudo, T. Yoshida, S. Kondo, B. G. Christensen, *J. Antibiot.* **1988**, *41*, 1154-1157; c) H. C. Neu in *The Chemistry of β-Lactams*, (Eds.: M. I. Page), Blackie, Glasgow, **1992**, pp. 101-128.

[3] a) B. Ruhland, A. Bhandari, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1996**, *118*, 253-254; b) B. Ruhland, A. Bombrun, M. A. Gallop, *J. Org. Chem.* **1997**, *62*, 7820-7826; c) Y. Pei, R. A. Houghten, J. S. Kiely, *Tetrahedron Lett.* **1997**, *38*, 3349-3352; d) E. G. Matta, *ibid.* **1997**, *38*, 6335-6338; e) V. Molteni, R. Annunziata, H. Cinquini, F. Cozzi, M. Benaglia, *ibid.* **1998**, *39*, 1257-1260; f) M. Benaglia, M. Cinquini, F. Cozzi, *Tetrahedron Lett.*, **1999**, *40*, 2019-2020; g) R. Singh, J. M. Nuss, *Tetrahedron Lett.*, **1999**, *40*, 1249-1252.

[4] B. Furman, R. Thürmer, Z. Kałuża, R. Łysek, W. Voelter, M. Chmielewski, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1121-1123.

[5] a) S. H. DeWitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. Reynolds Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA*, **1993**, *90*, 6909-6913; b) B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.*, **1996**, 37, 937-940; c) S. A. Kolodziej, B. C. Hamper, *Tetrahedron Lett.*, **1996**, *37*, 5277-5280; d) L. F. Tietze, A. Steinmetz, F. Balkenhohl, *Bioorg. & Med. Chem. Lett.*, **1997**, *7*, 1303-1306; e) J. Matthews, R. A. Rivero, *J. Org. Chem.*, **1997**, *62*, 6090-6092; f) S. W. Kim, S. Y. Ahn, J. S. Koh, J. H. Lee, S. Ro, H. Y. Cho, *Tetrahedron Lett.*, **1997**, *38*, 4603-4606; g) P. P. Fantauzzi, K. M. Yager, *Tetrahedron Lett.*, **1998**, *39*, 1291-1294; h) P. ten Holte, L. Thijs, B. Zwanenburg, *Tetrahedron Lett.*, **1998**, *39*, 7407-7410; i) A. R. Katritzky, S. A. Belyakov, Y. Fang, J. S. Kiely, *Tetrahedron Lett.*, **1998**, *39*, 8051-8054; j) J. Stadlwieser, E. P. Ellmerer-Müller, A. Takó, N. Maslouh, W. Bannwarth, *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 1402-1404; k) H.-P. Buchstaller, *Tetrahedron*, **1998**, *54*, 3465-3470.

[6] a) J. H. van Maarseveen, J. A. J. den Hartog, V. Engelen, E. Finner, G. Visser, C. G. Kruse, *Tetrahedron Lett.*, **1996**, *37*, 8249-8252; b) J. J. N. Veerman, J. H. van Maarseveen, G. M. Visser, C. G. Kruse, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *Eur. J. Org. Chem.*, **1998**, 2583-2589; c) J.-U. Peters, S. Blechert, *Synlett*, **1997**, 348-350; d) J. Pernerstorfer, M. Schuster, S. Blechert, *Chem. Commun.*, **1997**, 1949-1950; e) A. D. Piscopio, J. F. Miller, K. Koch, *Tetrahedron Lett.*, **1997**, *38*, 7143-7146; f) A. D. Piscopio, J. F. Miller, K. Koch, *Tetrahedron Lett.*, **1998**, *39*, 2667-2670.

[7] a) K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature*, **1997**, *387*, 268-272; b) K. C. Nicolaou, J. Pastor, N. Winssinger, F. J. Murphy, *J. Am. Chem. Soc.*, **1998**, *120*, 5132-5133.

[8] a) Z. Kałuża, S.-H. Park, *Synlett*, **1996**, 895-896; b) Z. Kałuża, R. Łysek, *Tetrahedron: Asymmetry*, **1997**, *8*, 2553-2560; c) Z. Kałuża, *Tetrahedron Lett.*, **1998**, *39*, 8349-8353; d) Z. Kałuża, *Tetrahedron Lett.*, **1999**, *40*, 1025-1026.

[9] a) S. Hanessian, F. Xie, *Tetrahedron Lett.*, **1998**, *39*, 733-736; b) S. Hanessian, F. Xie, *Tetrahedron Lett.*, **1998**, *39*, 737-740.

[10] a) S. Hanessian, H. K. Huynh, *Synlett*, **1999**, 102-104; b) S. Wendeborn, A. De Mesmaeker, W. K. D. Brill, *Synlett*, **1998**, 865-868.

[11] Z. Kałuża, B. Furman, M. Patel, M. Chmielewski, *Tetrahedron: Asymmetry*, **1994**, *5*, 2179-2186.