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ScienceDirect
Mendeleev Commun., 2012, **22**, 157–158

Mendeleev
Communications

Synthesis of chlorophyll *a* glycoconjugates using olefin cross-metathesis

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DOI: 10.1016/j.mencom.2012.05.016

Chlorophyll *a* glycoconjugates were obtained by cross-metathesis between olefin moieties of chlorophyll derivatives and allyl-β-galactopyranoside tetraacetate.

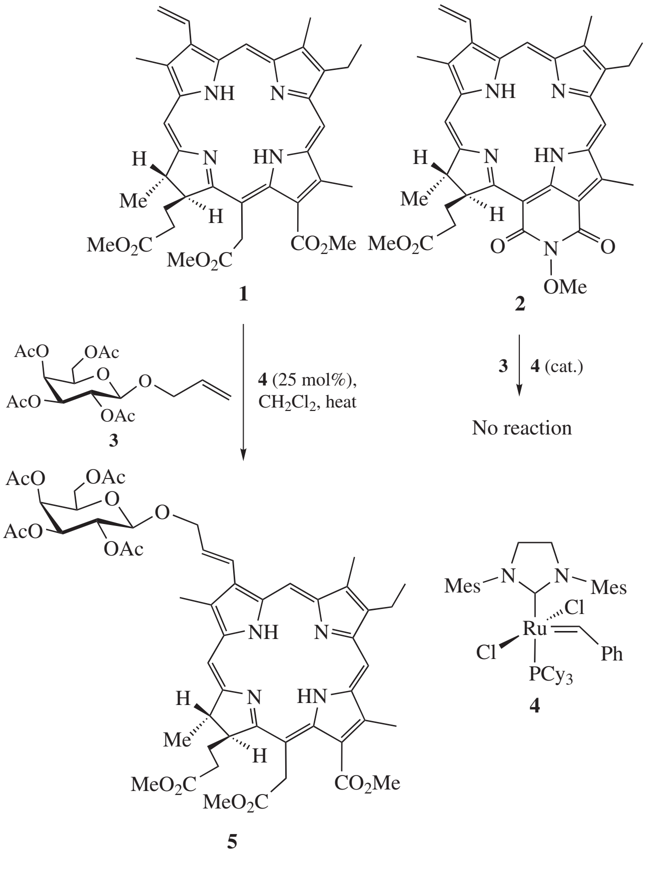
The photodynamic therapy (PDT) of cancer is a noninvasive method for the treatment of malignant neoplasms, in which two separately introduced non-toxic agents, *i.e.* a photosensitizer (PS) and laser radiation, meet in a target cell to generate cytotoxic compounds that destroy vitally important structures in tumour cells causing their death.[1–5] Natural chlorophyll based PSs have been of special interest in recent years, since their therapeutic absorption window (660–800 nm) opens up new prospects for diagnostics and treatment of malignant tumors.[6–8]

It seems reasonable to further enhance PDT efficiency by creating target PSs with such ligands for which the surface of tumor cells has specific receptors.[9–11] Tumor cells manifest high expression of galectins, *i.e.* proteins having a carbohydrate-recognizing domain with high affinity to β-galactosides.[12–14] Bonding of some sugars to porphyrins and their analogues ensures that such conjugates would specifically interact with cell galectins.[15–20]

In this study, we implemented an efficient method for synthesising glycoconjugates in a series of chlorophyll *a* derivatives, based on the olefin–olefin cross-metathesis (Scheme 1). The presence of a vinyl group in pyrrole ring A of chlorophyll macrocycle is a good challenge for using such a strategy: previously, β-vinyl group of porphyrins and chlorins was successfully involved in the cross-metathesis with various types of alkenes in the presence of second-generation Grubbs ruthenium catalyst.[21–23]

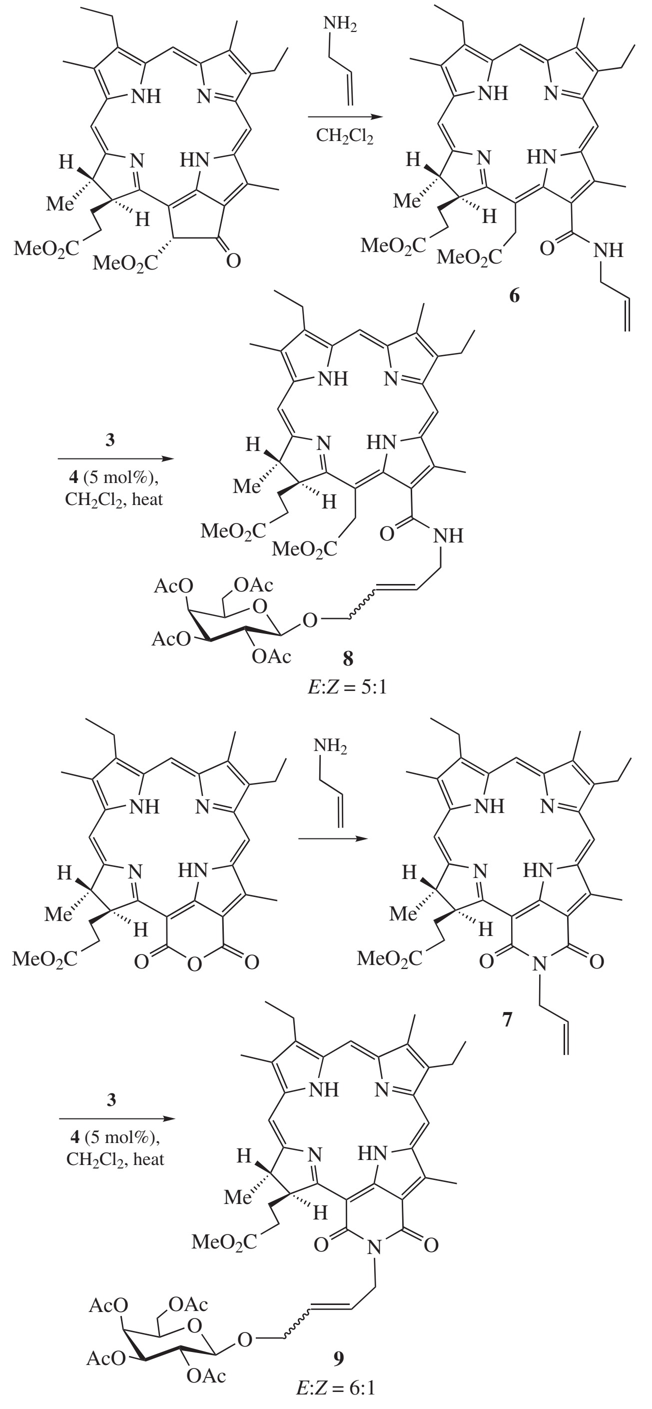
Herein, we attempted to obtain glycoconjugates from chlorin e_6 trimethyl ester **1** and *N*-methoxypurpurinimide methyl ester **2**,[24] which were coupled with allyl-β-D-galactopyranoside tetraacetate **3**[19] in the presence of catalyst **4** (see Scheme 1). Cross-metathesis between chlorin **1** and galactoside **3** in the presence of 5 mol% of second-generation Grubbs catalyst **4** resulted in only minor conversion of the reactants and the yield of the target galactosylchlorin **5** did not exceed 5%. A study of this reaction has shown that the highest yield of glycoconjugate **5** (40%) is attained by refluxing chlorin **1** with allylgalactoside **3** in dichloromethane for 16 h in the presence of 25 mol% catalyst **4**, while greater catalyst loading did not affect considerably the conversion of chlorin **1**. This reaction occurred stereoselectively to produce a double bond in *E*-configuration and gave no side products, which facilitated the chromatographic separation of the target product and unreacted chlorin **1** suitable for reuse.

The moderate yield of glycosylchlorin **5** is apparently caused by steric hindrance created by the macrocycle. As a result, fast self-metathesis of highly reactive allyl galactoside **3** occurred preferably. Unfortunately, such reaction conditions proved to be inefficient in the case of purpurinimide **2**, when the target conjugate was not obtained. We explain this fact by the electron-withdrawing properties of the imide exocycle that lowers the electron density on the vinyl group thus deactivating it (*cf.* ref. 23).



Scheme 1

Compounds **6** and **7** (Scheme 2) seemed other good candidates for our purpose. The allyl group at the pyrrole ring C of compound **6** was introduced by opening exocycle E in the mesopheophorbide precursor on treatment with allylamine. Hydrogenation of the vinyl group at pyrrole ring A of methylpheophorbide to an ethyl group was dictated by the necessity to introduce a carbohydrate moiety regioselectively at position 13 of the macrocycle. The reaction of allylamide **6** with allyl-β-D-galactopyranoside tetraacetate **3** in 1:5 ratio in the presence of catalyst **4** (5 mol%) for 4 h gave conjugate **8** in a high yield. An excess of one of the reactants was required to shift the equilibrium towards the



Scheme 2

reaction product and to lower formation of homodimers (see ref. 25). Note that in this case the reaction occurred with lower stereoselectivity than outlined in Scheme 1 giving two isomers (*E*/*Z*) of compound **8** in 5:1 ratio (NMR data) in 80% overall yield. Using preparative TLC, we isolated the major product (*E*-isomer) which had lower chromatographic mobility.

A similar cross-metathesis of purpurinimide **7** with allyl-β-D-galactopyranoside tetraacetate **3** resulted in the target glycoconjugate **9** in a high yield. In this case, the ratio of *E*/*Z* isomers of conjugate **9** was 6:1, while the major *E*-isomer was isolated in 62% yield. Thus, we have shown that the efficiency of cross-metathesis depends on the position of the terminal double bond in the macrocycle and on the distance between these.

Removal of protective acetyl groups in compounds **5**, **8** and **9** on treatment with sodium methoxide in a MeOH/CH_2Cl_2 system gave the corresponding glycoconjugates in 75–85% yields. The glycochlorins that we synthesised are currently undergoing bioassays in order to find the most efficient compound for creating the target PS for the PDT of cancer.

The preliminary *in vitro* studies of the obtained compounds revealed that deacetylated conjugate **5** possessed the highest photoinduced cytotoxicity. Its photophysical properties, including quantum yield of fluorescence and singlet oxygen production are currently studied.

This study was supported by the RF President programme for state support of young Russian scientists (Ph.D.) (grant no. MK-2016.2011.3), Russian Foundation for Basic Research (grant no. 11-03-00620-a) and the Federal goal-oriented programme ‘Research and Developments on Priority Directions of Evolution of the Scientific and Technological Complex of Russia for 2007–2012’ (state contract no. 16.512.11.2008 of 10.02.2011).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.05.016.

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Received: 26th October 2011; Com. 11/3824