Synthesis of peptides containing a combination of free and 2-trans-cyclooctene carbamate protected lysine residues

Doelman, W.; Ligthart, N.A.M.; Plassche, M.A.T. van de; Geus, M.A.R. de; Reinalda, L.; Isendoorn, M.M.E.; ... ; Kasteren, S.I. van

ChemBioChem

Research Article
doi.org/10.1002/cbic.202300786

Chemistry Europe
European Chemical Societies Publishing

www.chembiochem.org

Synthesis of Peptides Containing a Combination of Free and 2-*trans*-Cyclooctene Carbamate Protected Lysine Residues

W. Doelman,*[a] N. A. M. Ligthart,[a] M. A. T. van de Plassche,[a] M. A. R. de Geus,[a] L. Reinalda,[a] M. M. E. Isendoorn,[a] D. V. Filippov,[a] and S. I. van Kasteren*[a]

The allylic *trans*-cyclooctene (TCO) functionality facilitates powerful control over the spatiotemporal activity of bio-active molecules, enabling precision targeting of druglike and imaging modalities. However, the introduction of this function onto molecules remains chemically challenging, particularly for peptides. Modification with TCOs of this important class of biomolecules remains a challenge, primarily due to the sensitivity of the TCO group to the strong acids typically used in global deprotection during solid phase peptide synthesis. Here, we present a novel synthetic approach to site-selectively introduce TCO-groups in peptides. Our approach utilizes azide groups to mask amine functions, enabling selective introduction of the TCO on a single lysine residue. Staudinger reduction of the azides back to the corresponding amines proceeds without disturbing the sensitive TCO. We show that using our method, we can produce TCO-inactivated antigenic peptides of previously unseen complexity.

Introduction

Dissociative bio-orthogonal reactions are a quickly developing field of chemical biology.[1] Among the currently known dissociative bio-orthogonal reactions, the "click-to-release"-reaction, first demonstrated by Robillard,[2] has become one of the main reactions of choice. The "click" part of the name is the inverse electron demand Diels-Alder (IEDDA) reaction between a 2-*trans*-cyclooctene (2-TCO) and a 1,2,4,5-tetrazine. In this reaction an unstable dihydropyridazine intermediate is formed, which can eliminate the leaving group on the allylic position of the TCO, "releasing" the molecule. Using this reaction, spatial and/or temporal control over biological functions, such as receptor-ligand interactions[3] or cytotoxic activity[2,4] has been achieved. The "click-to-release" reaction is especially useful for biological applications as it has fast kinetics,[5] while the tetrazine reagents have low toxicity and good bioavailability.[4,6]

Allylic *trans*-cyclooctenes have also been used for the protection of peptides. We previously produced a T-cell epitope containing a TCO-protected lysine, shielding the epitope from recognition by its cognate T-cell clone.[7] Addition of tetrazine (in vitro or *in vivo)* allowed for the controlled activation of the T-cell in space and time.[8] Further expansion of this approach to more complicated peptides has been hindered by the extreme acid-lability of the trans-cyclooctene moiety.[9,10] As any concentration of trifluoroacetic acid led to the partial deprotection and/or isomerization to the unreactive *cis*-isomer,[3,10] on-resin modification of lysine residues during Fmoc-SPPS (solid phase peptide synthesis) with TCO was not viable. Post-synthetic modification of the peptide, using a compatible protection group to temporarily block the N-terminus (Figure 1A) allowed for the synthesis of peptides containing a single lysine residue, but lacked the selectivity required for the modification of a single lysine in peptides containing multiple.

A synthetic approach, whereby (longer) peptides can be synthesized that contain both a 2-TCO-protected lysine, as well as unreacted lysines, is therefore an unmet chemical need. Particularly, as this would allow the extension of the above T-cell activation study, to also study the processing of long peptide antigens by antigen presenting cells, as was previously done using a Staudinger-reduction approach.[11] La-Venia *et al.*[10] (Figure 1B) have developed such an approach for the introduction of a non-allylic TCO group (4-TCO) on short peptides. However, their method relies on NaOH mediated release of the peptide from the solid support, an often low yielding method for longer peptides.[12,13] We therefore looked for an alternative strategy that could utilize the regular, highly efficient acidic resin cleavage used in standard Fmoc-SPPS. It was here postulated that an azide protection strategy could be used (Figure 1C). Lysine residues not intended for 2-TCO protection could be introduced as the commercially available azidolysine building block, while the N-terminus could be protected in the form of the α-azido acid. The azide is stable during basic Fmoc-deprotection and acidic resin cleavage,[14] and can be reduced to the corresponding amine using a mild phosphine reduction.[15,16] In this paper we demonstrate the utility of azide-protection in the synthesis of 2-TCO modified

[a] *W. Doelman, N. A. M. Ligthart, M. A. T. van de Plassche, M. A. R. de Geus, L. Reinalda, M. M. E. Isendoorn, D. V. Filippov, S. I. van Kasteren*
Leiden Institute of Chemistry, Leiden, the Netherlands
E-mail: s.i.van.kasteren@chem.leidenuniv.nl
w.doelman@lic.leidenuniv.nl

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cbic.202300786

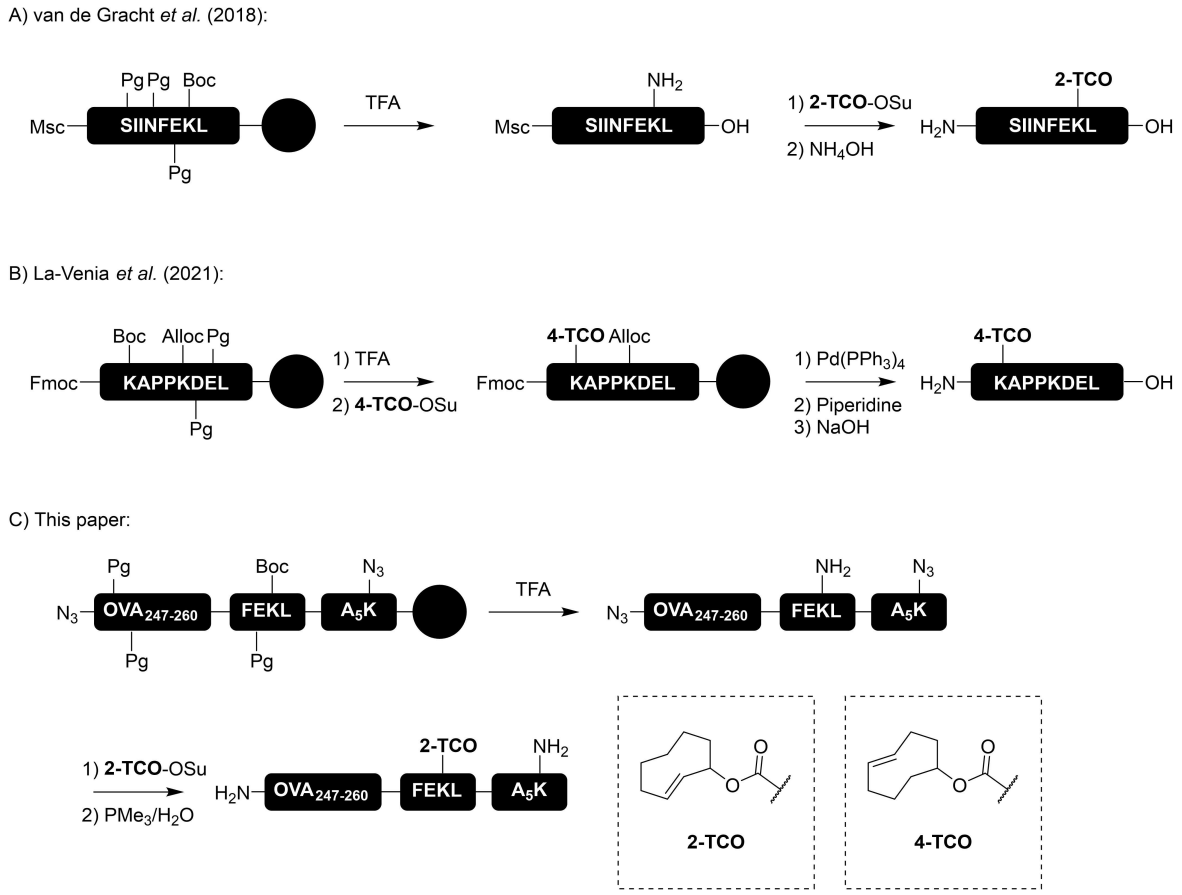
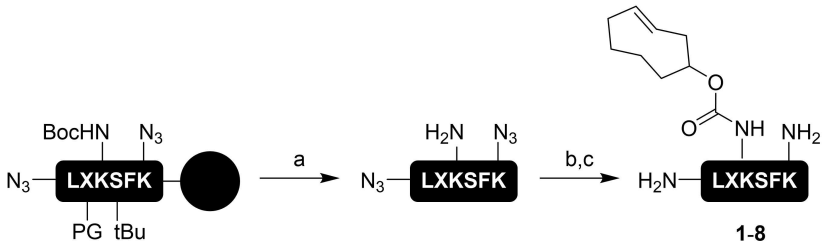


Figure 1. Overview of published methods to synthesize TCO functionalized peptides. A) Hybrid synthesis using the base-labile Msc group as temporary N-terminal protecting group.[7] b) Full on-resin method published by Vrabel to introduce 4-TCO groups onto peptides.[10] c) Novel approach described in this paper.

Table 1. Exploring the scope of the TCO modification/Staudinger reduction approach by screening several amino acid functions. Reagents and conditions: a) TFA, TIS, H_2O; b) TCO-OSu, DiPEA, DMF; c) PMe_3, H_2O.



#	Peptide sequence	Yield (%)
1	LYK(TCO)SFK-NH_2 (**1**)	13
2	LEK(TCO)SFK-NH_2 (**2**)	9
3	LHK(TCO)SFK-NH_2 (**3**)	10
4	LWK(TCO)SFK-NH_2 (**4**)	11
5	LRK(TCO)SFK-NH_2 (**5**)	11
6	LKK(TCO)SFK-NH_2 (**6**)	6
7	LCK(TCO)SFK-NH_2 (**7**)	4
8	LN(GlcNAc)K(TCO)SFK-NH_2 (**8**)	5

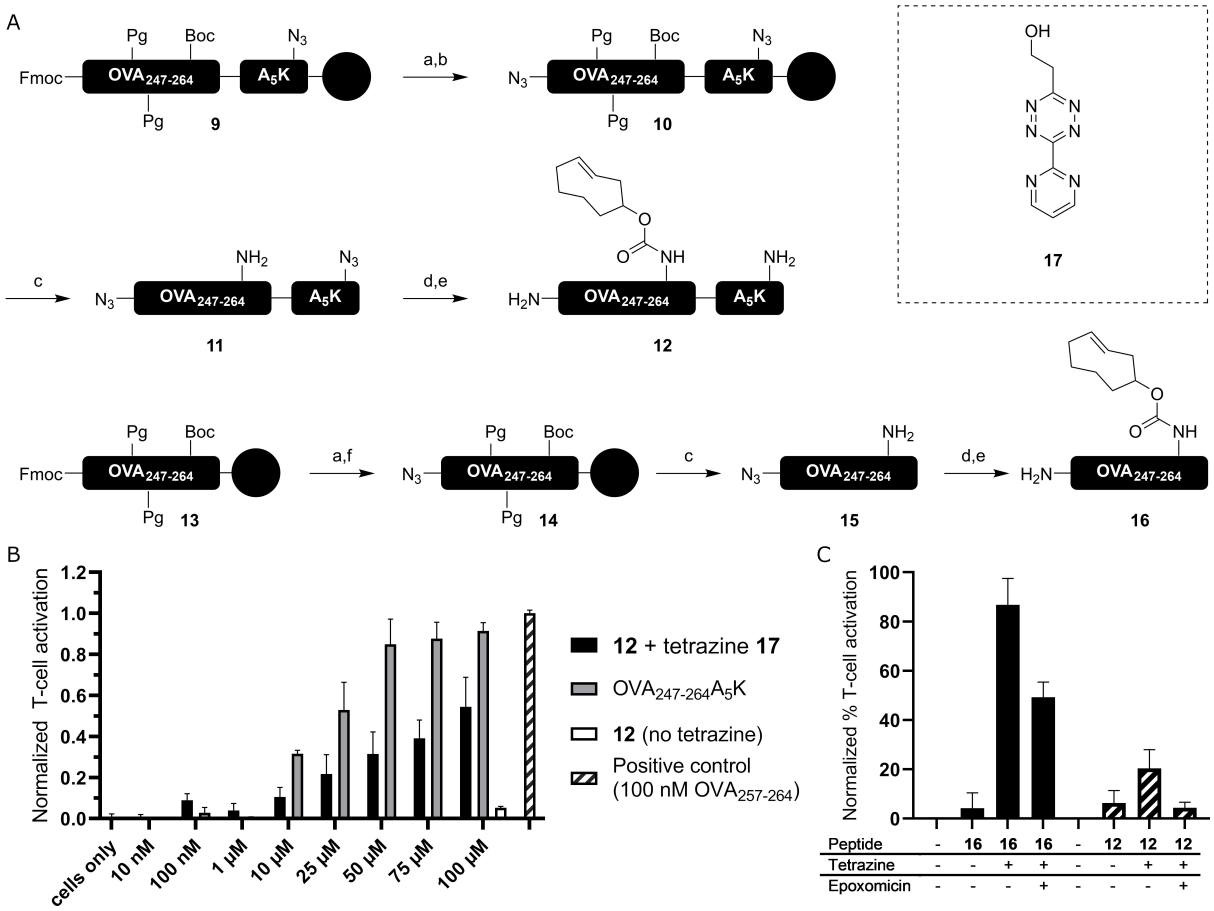


Figure 2. A) synthesis of TCO-protected antigenic peptides **12** and **16**. Reagents and conditions: a) 20% (v/v) piperidine, DMF b) ISA·H_2SO_4, DiPEA, DMF c) TFA, TIS, H_2O d) TCO-OSu, DiPEA, DMF e) PMe_3, H_2O f) ISA·H_2SO_4, K_2CO_3, H_2O. B) Comparison between dose-response observed for non-caged $OVA_{247-264}A_5K$ compared with caged peptide **12**, in the presence and absence of tetrazine **17**. C) Effect of epoxomicin inhibition of the proteasome on the cross-presentation of TCO-protected $OVA_{247-264}$ (**16**) and TCO-protected $OVA_{247-264}A_5K$ (**12**).

peptides, by synthesizing several TCO-modified peptides of unprecedented complexity, including a model conjugate vaccine.

Results and discussion

As the synthetic strategy that we envisioned here required the introduction of the TCO moiety on partially protected peptides in solution, we first set out to evaluate the scope of this approach on a series of model peptides. We envisioned to use a simple hexapeptide sequence (LXKSFK, where X represents several amino acids) where the C-terminal lysine residue, as well as the N-terminal amine, would be masked as azides, leaving the central lysine residue free for TCO modification. For the amino acid on position X we chose several amino acid functionalities that could be expected to hinder the introduction of the TCO moiety, either by bearing highly reactive nucleophiles (eg. Cys) or by introducing steric bulk (eg. Trp).

We also sought to streamline the synthetic procedure compared to our previously reported synthesis of TCO modified peptides, which involved the HPLC purification of the partially protected intermediate after resin liberation. To reduce the amount of time and solvent consuming RP-HPLC purification steps required, we envisioned a protocol were several key steps could be carried out in succession without intermediate purification. We were curious if not only the reaction of the peptide with the *trans*-cyclooctene hydroxysuccinimide carbonate (TCO-OSu) could be performed on the crude peptide obtained after resin liberation, but also if the following Staudinger reduction could be carried out in the same pot.

We started our investigation with a test peptide containing a tyrosine residue on the X position (table 1, entry 1). The phenol functionality of tyrosine is not expected to hinder the synthesis, so we can use this peptide as a benchmark for the method. We commenced with SPPS synthesis of the sequence, where the C-terminal lysine was introduced as azido-norleucine and the N-terminal amino acid was introduced as commercially available α-azido-L-leucine. Resin liberation and deprotection of the acid labile protective groups was carried out using standard conditions (95 : 2.5 : 2.5 TFA/TIS/H_2O) and the crude peptide was recovered by precipitation from ice cold diethyl ether. The crude peptides was then transferred to a round-bottom flask, were residual TFA and water were removed under reduced pressure. A solution of TCO-OSu and DiPEA in DMF was added and the reaction was monitored by LC–MS analysis. Full

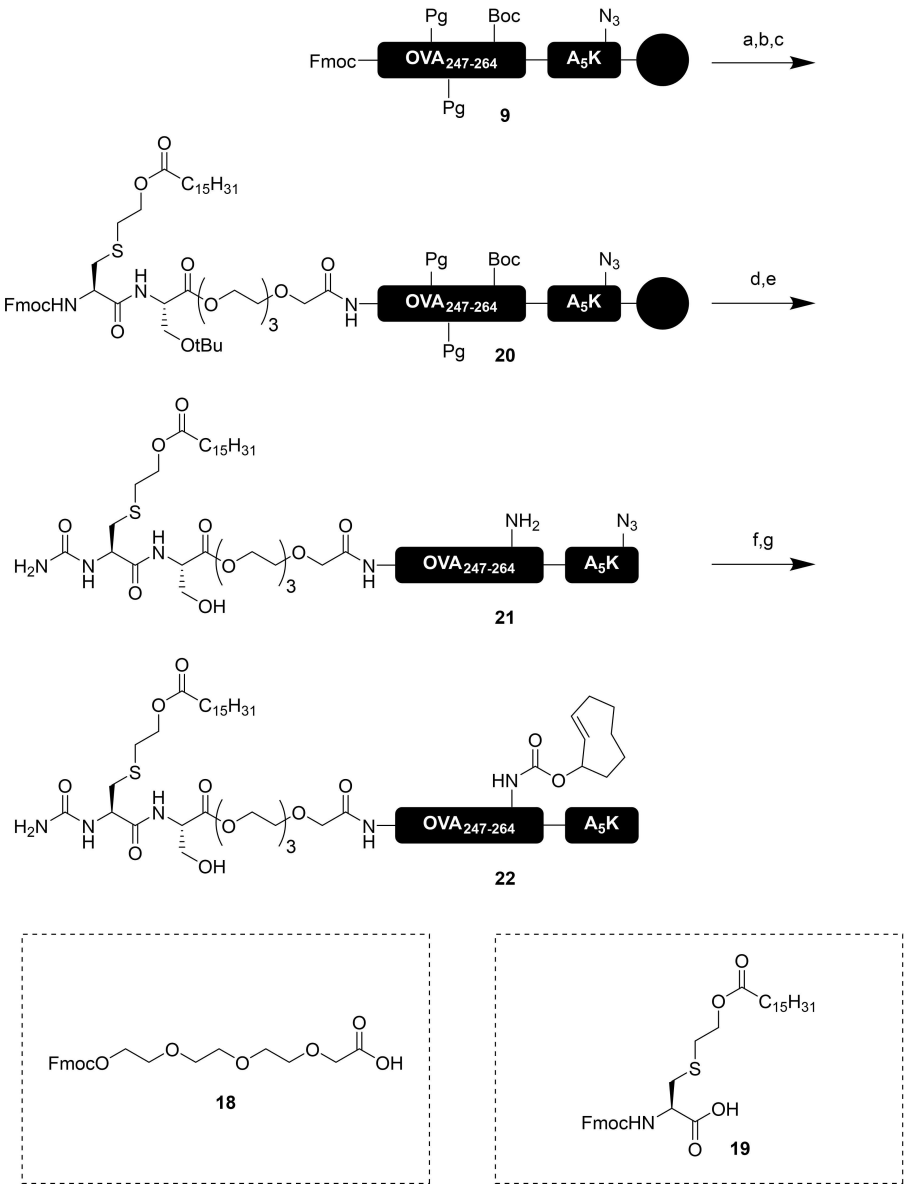


Figure 3. Synthesis of antigenic peptide **22** containing the hTLR2 ligand mini-UPam. Reagents and conditions: a) i) 20% (v/v) piperidine, DMF ii) **18**, HCTU, DiPEA, DMF b) i) 20% (v/v) piperidine, DMF ii) Fmoc-Ser(tBu)-OH, DIC, DMAP, DMF c) i) 20% (v/v) piperidine, DMF ii) **19**, HCTU, DiPEA, DMF d) i) 20% (v/v) piperidine, DMF ii) TMS-NCO, iPrOH, DCM e) TFA, TIS, H_2O f) TCO-Osu, DiPEA, DMF g) PMe_3, H_2O, DMF.

consumption of the starting material was observed after two hours. Staudinger reduction of the azide groups was then initiated by the addition of water and trimethylphosphine, resulting in the formation of the desired TCO-protected peptide. The peptide was recovered from solution by precipitation from diethyl ether, and RP-HPLC yielded the peptide in 13% yield (Table 1, entry 1). Further characterization by LC–MS, as well as a decaging experiment with dimethyltetrazine (Figure S1), proved full retention of the *trans* configuration of the cyclooctene.

Next, peptides containing a carboxylate nucleophile in the form of glutamic acid (entry 2), or competing *N*-nucleophiles like histidine (entry 3), tryptophan (entry 4) or arginine (entry 5) were evaluated. All of these reactive amino acid residues posed no hinderance to the synthesis and the resulting peptides were isolated in similar yields. A peptide containing an additional azide-protected lysine residue (entry 6) could also be converted into the desired peptide in a facile manner, showing that the Staudinger reduction step is not limited to the unmasking of two amines. To our further delight, a peptide containing cysteine (entry 7), a potentially troublesome nucleophilic residue, also yielded the desired peptide, although at somewhat lower yield. Finally, since TCO is a rather bulky and hydrophobic moiety, the effect of a large, hydrophilic group next to the target lysine, in the form of a GlcNAc modified asparagine residue, was evaluated (entry 8). Gratifyingly, the TCO introduction proceeded smoothly, and this peptide could also be obtained without encountering major obstacles.

Having shown that the method is fully compatible with peptides containing a wide variety of common functionalities,

we next applied it to the synthesis of antigenic peptides. As we have previously reported, the lysine residue in the $CD8^+$ T-cell specific epitope $OVA_{257-264}$ (SIINFEKL) is required for T-cell activation.[11] When this residue is blocked by an allylic TCO carbamate, the peptide is incapable of T-cell activation; bio-orthogonal click-and-release with a tetrazine reagent fully restores antigenic potential.[7] Here, we looked to apply this same approach to the study of the commonly used N- and C-terminally extended form of this peptide, $OVA_{247-264}A_5K$, bearing an additional 10 amino acids on the N-terminus and a pentaalanyl-lysinyl spacer on the C-terminus.[17]

Synthesis of this peptide commenced by standard SPPS assembly of resin-bound peptide **9**, with the C-terminal lysine introduced as the azido-protected azidonorleucine. The protection of the N-terminus was achieved by an on-resin diazotransfer reaction, using a modified literature procedure.[18] This transformation employed the bisulfate salt of imidazole-sulfuryl azide ($ISA{\cdot}H_2SO_4$) in DMF, yielding intermediate **10**. This peptide was liberated from the resin using a standard TFA cocktail, deprotecting all protecting groups except for the azide functions; precipitation from cold diethyl ether followed by rigorous co-evaporation with toluene insured peptide **11** was free from residual TFA. The introduction of the TCO function and azide reduction were carried out the same as described for the test peptides (*vide supra*) LC–MS indicated complete consumption of starting material **11** and formation of the TCO-modified peptide after two hours of reaction with TCO-OSu. The Staudinger reduction was carried out immediately in the same pot and after one hour, LC–MS confirmed the consumption of the azide-protected intermediate and the formation of desired product **12**. Reverse-phase HPLC yielded this peptide in 5.4%. In a similar manner, TCO-protected $OVA_{247-264}$ (**16**) could also be produced. Briefly, the *N*-terminal amine of resin bound peptide **13** was also masked in the form of an azide. The previously described conditions using $ISA{\cdot}H_2SO_4$ in DMF afforded poor conversion. Luckily, an alternative on-resin diazotransfer method, using the same reagent in aqueous medium, did afford good conversion.[19] Liberation with TFA afforded crude **15**, which was subjected to the one pot TCO-introduction/Staudinger reduction procedure. This procedure yielded peptide **16** after RP-HPLC, although in rather low yield, likely owing to the poor solubility of this molecule.

We have previously shown that $OVA_{247-264}$ bearing a bio-orthogonally protected lysine can still be processed and presented in the H2-K^b murine MHC–I,[8,11] but for the C-terminally extended $OVA_{247-264}A_5K$ peptide it is unknown whether correct processing and presentation can take place when the critical lysine residue is masked. Therefore, we evaluated peptide **12** in a cross-presentation assay.[7] In this assay, the D1 DC cell-line[20] was used as the antigen presenting cell (APC). D1 cells were incubated with various concentration of peptide **12** or the non-TCO protected control for 2 hours, after which the cells were washed and 10 μM of tetrazine **17** was added for 45 minutes. Then, B3Z T-cells[21] were added and T-cell activation was determined by a colorimetric LacZ assay (Figure 2B). We found that, in the absence of tetrazine, negligible T-cell activation was seen at 100 μM concentration of **12**. However, in the presence of tetrazine **17**, a clear dose-response correlation between the observed T-cell response and the concentration of peptide **12** was observed. The observed level of T-cell activation after uncaging peptide **12** was lower than the response against non-caged $OVA_{247-264}A_5K$, with about 40% of the expected T-cell response observed at 50 μM. Whether this is due to differences in peptide uptake or processing remains to be investigated.

With this new tool for the exploration of cross-presentation mechanism in hand, we decided to study the effect of proteasome inhibition on the level of cross-presentation of **12** and **16**. It has been shown that the proteasome is crucial for the liberation of the C-terminus of MHC class I restricted epitopes, but less so for the N-terminal side.[17] We first showed that inhibition of the proteasome using Epoxomicin has indeed no effect on the level of T-cell activation seen for $OVA_{247-264}$ but diminishes the level of T-cell activation for $OVA_{247-264}A_5K$ (Figure S2). Next, we evaluated the sensitivity of the cross-presentation of the TCO-caged peptides **12** and **16** towards epoxomicin treatment (Figure 2C). As expected, the C-terminally free TCO-protected peptide **16** shows little T-cell activation in the absence of tetrazine, and nearly full recovery of signal when tetrazine **17** is added. When tetrazine **17** and epoxomicin are given simultaneously, an unexpected drop in activation is seen, but the signal still remains above baseline, indicating antigen presentation is still taking place. Repeating this experiment with the C-terminally extended peptide **12** shows the expected result: T-cell activation seen in the presence of epoxomicin, after tetrazine-mediated uncaging, remains at background level.

As a final chemical challenge, we wanted to further test the ability of this new method to produce peptides that were previously inaccessible. To this end, we decided to further extend peptide **12** into a TLR-conjugate antigenic peptide. Antigenic peptides covalently linked to TLR ligands can be used to induce a stronger immune response, and are actively investigated as novel vaccines.[22,23] Here, we produce a peptide incorporating the hTLR2 ligand mini-Upam, previously described by van de Ende *et al.*[24] The sensitivity of the palmitoyl ester in this molecule to nucleophilic bases makes the synthesis of such a conjugate impossible using our previously disclosed synthesis of TCO protected peptides, but no such limitation should exist for this novel method.

Synthesis of this construct (Figure 3) started from resin bound peptide **9**. For the introduction of the TLR ligand, the literature procedure was followed. Briefly, the resin bound peptide was first extended with PEG linker **18**. Subsequently, a serine derivative was coupled to the free hydroxyl using DIC/DMAP. This was followed by the coupling of palmitoyilated building block **19** under standard conditions. Finally, after Fmoc cleavage, the N-terminal urea was introduced using TMS-isocyanate and the peptide was liberated from the solid support, resulting in crude peptide **21**. Introduction of the TCO onto the unprotected lysine residue proceeded smoothly. After LC–MS confirmed full conversion, Staudinger reduction in the same pot unmasked the C-terminal lysine, producing the desired, TCO modified TLR-conjugated peptide, which could be

isolated using RP-HPLC in a facile manner. This peptide represents, to our knowledge, the most complex molecule bearing a TCO moiety produced by chemical synthesis to date.

Conclusions

Since the first demonstration of the "click-to-release" concept a decade ago, *trans*-cyclooctene reagents have become a staple within the field of bioorthogonal uncaging chemistry. However, while their utility for both biochemical assays as well as clinical reality[25] has been thoroughly demonstrated, the introduction of this sensitive moiety into molecules by chemical synthesis remains a challenging endeavor. Here, we present a method to further expand the scope of allylic TCO protection in the field of peptide chemistry. Our method enables the synthesis of peptides bearing a combination of lysine residues protected with an allylic TCO and non-protected lysine residues, a feat not previously achieved with other protecting group strategies. We further demonstrated that the inclusion of reactive nucleophiles in the peptide does not hinder the synthesis in a meaningful way. We showed that this chemistry enables the synthesis of TCO-protected peptides of high complexity by synthesizing TCO-protected $OVA_{247\text{-}264}A_5K$ **12** and the lipopeptide derivative **22**.

We could demonstrate that the introduction of a TCO on the critical lysine residue of the $OVA_{247\text{-}264}A_5K$ peptide completely suppresses the ability of this antigenic peptide to induce T-cell activation. As demonstrated before for simpler systems, addition of tetrazine partially restored antigenic potential. Future research in our lab will focus on using this peptide as well as model conjugate vaccine **22** to better understand the kinetics of early T cell activation events.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

[1] J. Li, P. R. Chen, *Nat. Chem. Biol.* **2016**, *12*, 129–137.
[2] R. M. Versteegen, R. Rossin, W. ten Hoeve, H. M. Janssen, M. S. Robillard, *Angew. Chem. Int. Ed.* **2013**, *52*, 14112–14116.
[3] M. J. van de Graaff, T. Oosenbrug, M. H. S. Marqvorsen, C. R. Nascimento, M. A. R. de Geus, B. Manoury, M. E. Ressing, S. I. van Kasteren, *Bioconjug. Chem.* **2020**, *31*, 1685–1692.
[4] R. Rossin, R. M. Versteegen, J. Wu, A. Khasanov, H. J. Wessels, E. J. Steenbergen, W. ten Hoeve, H. M. Janssen, A. H. A. M. van Onzen, P. J. Hudson, M. S. Robillard, *Nat. Commun.* **2018**, *9*, 1–11.
[5] M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 13518–13519.
[6] G. Zhang, J. Li, R. Xie, X. Fan, Y. Liu, S. Zheng, Y. Ge, P. R. Chen, *ACS Cent. Sci.* **2016**, *2*, 325–331.
[7] A. M. F. van der Gracht, M. A. R. de Geus, M. G. M. Camps, T. J. Ruckwardt, A. J. C. Sarris, J. Bremmers, E. Maurits, J. B. Pawlak, M. M. Posthoorn, K. M. Bonger, D. V. Filippov, H. S. Overkleeft, M. S. Robillard, F. Ossendorp, S. I. van Kasteren, *ACS Chem. Biol.* **2018**, *13*, 1569–1576.
[8] N. A. M. Ligthart, M. A. R. de Geus, M. A. T. van de Plassche, D. Torres García, M. M. E. Isendoorn, L. Reinalda, D. Ofman, T. van Leeuwen, S. I. van Kasteren, *J. Am. Chem. Soc.* **2023**, *145*, 12630–12640.
[9] J. E. Nordlander, K. D. Kotian, D. E. Raff, F. G. Njoroge, J. J. Winemiller, G. F. Njoroge, J. J. Winemiller, *J. Am. Chem. Soc.* **1984**, *106*, 1427–1432.
[10] A. La–Venia, R. Dzijak, R. Rampmaier, M. Vrabel, *Chem. – A Eur. J.* **2021**, *27*, 13632–13641.
[11] J. B. Pawlak, G. P. P. Gential, T. J. Ruckwardt, J. S. Bremmers, N. J. Meeuwenoord, F. A. Ossendorp, H. S. Overkleeft, D. V. Filippov, S. I. van Kasteren, *Angew. Chem. Int. Ed.* **2015**, *54*, 5628–5631.
[12] P. Sieber, *Tetrahedron Lett.* **1987**, *28*, 2107–2110.
[13] J. Alsina, F. Albericio, *Pept. Sci.* **2003**, *71*, 454–477.
[14] J. T. Lundquist IV, J. C. Pelletier, *Org. Lett.* **2002**, *4*, 3219–3221.
[15] M. Meldal, M. A. Juliano, A. M. Jansson, *Tetrahedron Lett.* **1997**, *38*, 2531–2534.
[16] J. T. Lundquist IV, J. C. Pelletier, *Org. Lett.* **2001**, *3*, 781–783.
[17] S. Khan, M. S. Bijker, J. J. Weterings, H. J. Tanke, G. J. Adema, T. van Hall, J. W. Drijfhout, C. J. M. Melief, H. S. Overkleeft, G. A. van der Marel, D. V. Filippov, S. H. van der Burg, F. Ossendorp, *J. Biol. Chem.* **2007**, *282*, 21145–21159.
[18] M. B. Hansen, T. H. M. Van Gurp, J. C. M. van Hest, D. W. P. M. Löwik, *Org. Lett.* **2012**, *14*, 2330–2333.
[19] J. E. Marine, X. Liang, S. Song, J. G. Rudick, *Pept. Sci.* **2015**, *104*, 419–426.
[20] C. Winzler, P. Rovere, M. Rescigno, F. Granucci, G. Penna, L. Adorini, V. S. Zimmermann, J. Davoust, P. Ricciardi-Castagnoli, *J. Exp. Med.* **1997**, *185*, 317–328.
[21] J. Karttunen, N. Shastri, *Proc. Natl. Acad. Sci. U. S. A.* **1991**, *88*, 3972–3976.
[22] F. M. Speetjens, M. J. P. Welters, M. Slingerland, M. I. E. van Poelgeest, P. J. de Vos van Steenwijk, I. Roozen, S. Boekestijn, N. M. Loof, G. G. Zom, A. R. P. M. Valentijn, W. J. Krebber, N. J. Meeuwenoord, C. A. H. Janssen, C. J. M. Melief, G. A. van der Marel, D. V. Filippov, S. H. van der Burg, H. Gelderblom, F. Ossendorp, *J. Immunother. Cancer* **2022**, *10*, e005016.
[23] G. G. Zom, M. M. J. H. P. Willems, S. Khan, T. C. van der Sluis, J. W. Kleinovink, M. G. M. Camps, G. A. van der Marel, D. V. Filippov, C. J. M. Melief, F. Ossendorp, *J. Immunother. Cancer* **2018**, *6*, 1–13.
[24] T. C. van den Ende, J. M. M. Heuts, G. P. P. Gential, M. Visser, M. J. van de Graaff, N. I. Ho, W. Jiskoot, A. R. P. M. Valentijn, N. J. Meeuwenoord, H. S. Overkleeft, J. D. C. Codée, S. H. Burg, E. M. E. Verdegaal, G. A. Marel, F. Ossendorp, D. V. Filippov, *ChemBioChem* **2021**, *22*, 1215–1222.
[25] I. S. Srinivasan, N. A. Yee, M. Zakharian, M. Alečković, A. Mahmoodi, T.-H. Nguyen, J. M. Mejía Oneto, *bioRxiv* **2023**, 2023.03.28.534654.

Manuscript received: November 22, 2023
Revised manuscript received: December 20, 2023
Accepted manuscript online: December 21, 2023
Version of record online: January 17, 2024