One-Pot Isomerization−Cross Metathesis−Reduction (ICMR) Synthesis of Lipophilic Tetrapeptides

Mouhamad Jida,*,[†] Cecilia Betti,[†] Peter W. Schiller,[‡] Dirk Tourwé,[†] and Steven Ballet*,[†]

[†]Department of Organic Chemistry, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium
[‡]Department of Chemical Biology and Peptide Research, Clinical Research Institute of Montreal, 110 Avenue Des Pins Ouest, Montreal, Quebec H2W 1R7, Canada

Ⓢ *Supporting Information*

ABSTRACT: An efficient, versatile and rapid method toward homologue series of lipophilic tetrapeptide derivatives (herein, the opioid peptides H-TIPP-OH and H-DIPP-OH) is reported. High atom economy and a minimal number of synthetic steps resulted from a one-pot tandem isomerization-cross metathesis-reduction sequence (ICMR), applicable both in solution and solid phase methodology. The broadly applicable synthesis proceeds with short reaction times and simple work-up, as illustrated in this work for alkylated opioid tetrapeptides.

KEYWORDS: alkylated tetrapeptides, one-pot tandem reactions, isomerization-cross metathesis-reduction process (ICMR), Grubbs' second generation and Umicore M2 catalysts, solution and solid phase peptide synthesis
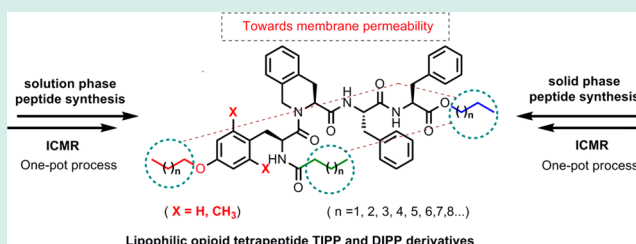
■ INTRODUCTION

In the last two decades, our laboratory has been particularly interested in the synthesis of novel potent, and receptor subtype selective opioid peptides.[1−3] The prototype peptide H-Tyr-Tic-Phe-Phe-OH (TIPP) displayed high δ receptor selectivity and antagonist activity (Figure 1).[2] Interestingly, the corresponding C-terminal amide TIPP-NH₂ as well as the 2′,6′-dimethyl-Tyr[1] (Dmt[1]) bearing analogue, DIPP-NH₂ (H-Dmt-Tic-Phe-Phe-NH₂, Figure 1), displayed a promising mixed μ-agonist/δ-antagonist profile, a pharmacological profile that, in contrast to the classical opioids, may lead to opioids with a diminished propensity to induce tolerance and physical dependence during a long-term treatment of pain by chronic administration.[2b]

As chain extension, with concomitant increased lipophilicity, represents one of the standard modifications available to medicinal chemists in search for an improved therapeutic profile of lead structures, our group wanted to verify the effect of (extended) alkyl side chains on the μ-agonist properties/δ-antagonist profiles of H-TIPP-OH/NH₂ and H-DIPP-OH/NH₂. As such, a large set of lipophilic tetrapeptide derivatives, based on the TIPP and DIPP sequences, containing an alkyl substituent on the N-, C-terminus, and side chain positions were synthesized. These peptide derivatives might diminish the intrinsic drawbacks of peptides as therapeutic agents and enhance gut-blood or blood-brain barrier (BBB) permeability. The latter property is the most cumbersome hurdle left for the TIPP or DIPP family of ligands.[1f]

To access the desired lipophilic tetrapeptides (TIPP and DIPP derivatives) in an efficient manner, we aimed to use a one-pot procedure following a cross metathesis−olefin reduction reaction on solid support or in solution.

Ruthenium-based olefin metathesis catalysts have provided routes toward new olefins that appear in a variety of valuable structures for pharmaceutical and material science.[4,5,4d,5b]

From the numerous catalysts that are available for metathesis reactions, catalysts **1** (Umicore M2 s generation) and **2** (Grubbs' second generation), depicted in Figure 2, were selected in this study. The Umicore M2 metathesis catalyst yields high E/Z selectivities, it is more resistant to harsh reaction conditions, as compared to the Grubbs II catalyst, shows increased activity upon temperature increase, and excellent stability to air and moisture.[6] However, when the catalysts are stressed by high temperatures, high dilution, and forced high turnovers, olefin isomerization has been reported in a few papers (vide infra).[5a,15] This isomerization could be turned to our advantage in the current study. As a consequence and driven by our interest in the synthesis of more lipophilic tetrapeptides bearing alkyl chains of variable length, we discovered a facile and rapid synthesis of novel TIPP- and DIPP-alkyl derivatives, in which the alkyl chain length varies, via a one-pot tandem isomerization-cross-metathesis-reduction sequence. A large set of N-terminus, C-terminus, and side-chain-derivatized lipopeptides was prepared in good overall yields and high purity using both a solution and solid phase parallel synthesis approach.
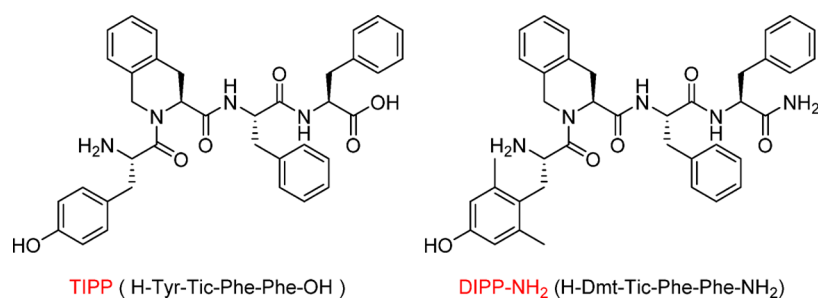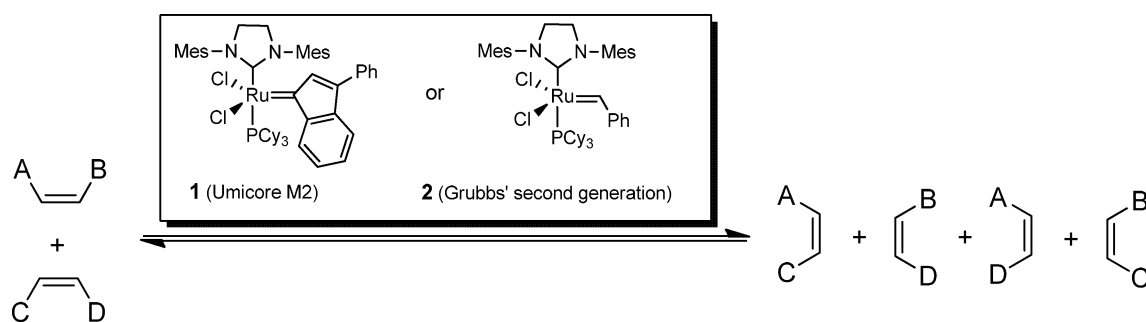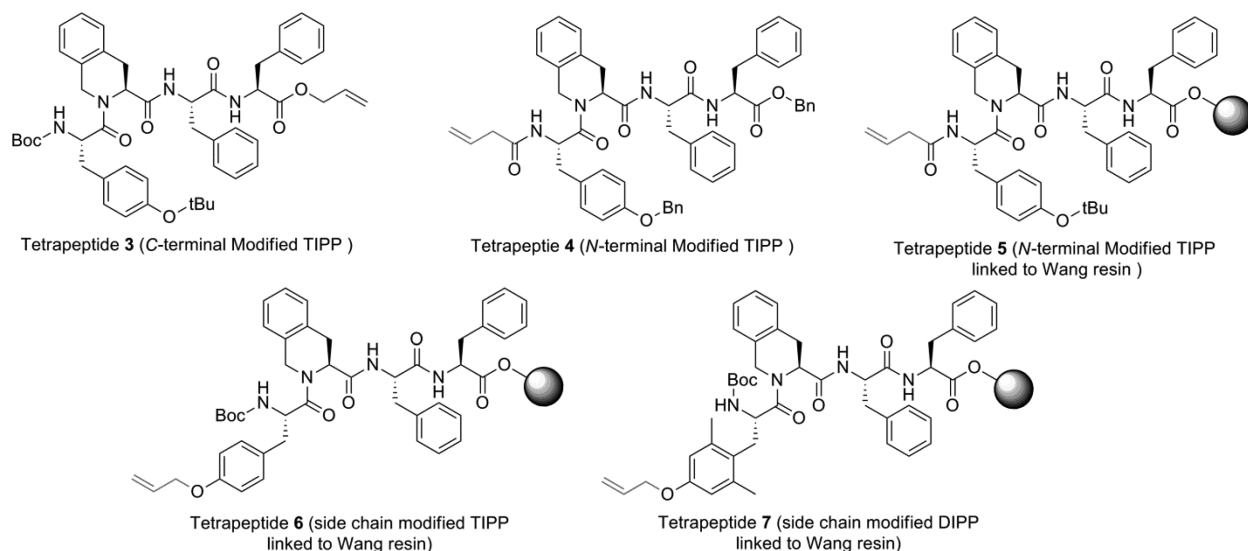
Figure 1. General structures of the tetrapeptides TIPP-OH and DIPP-NH$_2$ (μ-agonist/δ-antagonist opioid analgesics).

Figure 2. Cross-metathesis: Alkylidene swap between two acyclic olefins.

Figure 3. Structures of modified TIPP and DIPP tetrapeptides as precursors for the tandem ICMR reactions (isomerization−cross metathesis−reduction).

■ RESULT AND DISCUSSION

To achieve the synthesis of all desired peptide compounds, the tandem ICMR (isomerization/cross-metathesis/reduction reactions) was attempted in solution or on solid phase. First, precursors **3** and **4** (Figure 3) were prepared stepwise by solution phase peptide synthesis as outlined in Scheme 1 by use of propylphosphonic anhydride (T3P). This reagent, commonly used as a coupling agent, is a highly reactive water scavenger that offers several advantages over traditional reagents, such as low toxicity, commercial availability, a low price, low epimerization tendency and broad functional group tolerance. Moreover, it gives way to excellent purity and easy work up procedures thanks to the formation of water-soluble byproducts.[7] As can be noticed in Scheme 1, all peptide couplings take place with high yields (See Supporting Information for more detail).

Next, precursors **5**, **6**, and **7** (Figure 3) were synthesized on solid-phase. In general, solid phase organic synthesis (SPOS) is a rapidly expanding field which is being widely exploited in search for new peptide derivatization techniques to be used in medicinal chemistry and compatible with combinatorial technology.[8,9] This has permitted an extraordinary increase in the speed of synthesis through both work-up simplification and automation. Although solid-phase peptide synthesis (SPPS) is a well-established procedure, microwave-assisted SPPS has received attention since microwave irradiation can accelerate reaction rates, allow cumbersome couplings (e.g., *N*Me-amino acid couplings), and improve the purities and yields in SPPS.[10]

Scheme 1. Solution-Phase Synthesis of the CM Precursors H-Tyr-Tic-Phe-Phe-OAll (3) and 3-Butenoyl-Tyr-Tic-Phe-Phe-OH (4)
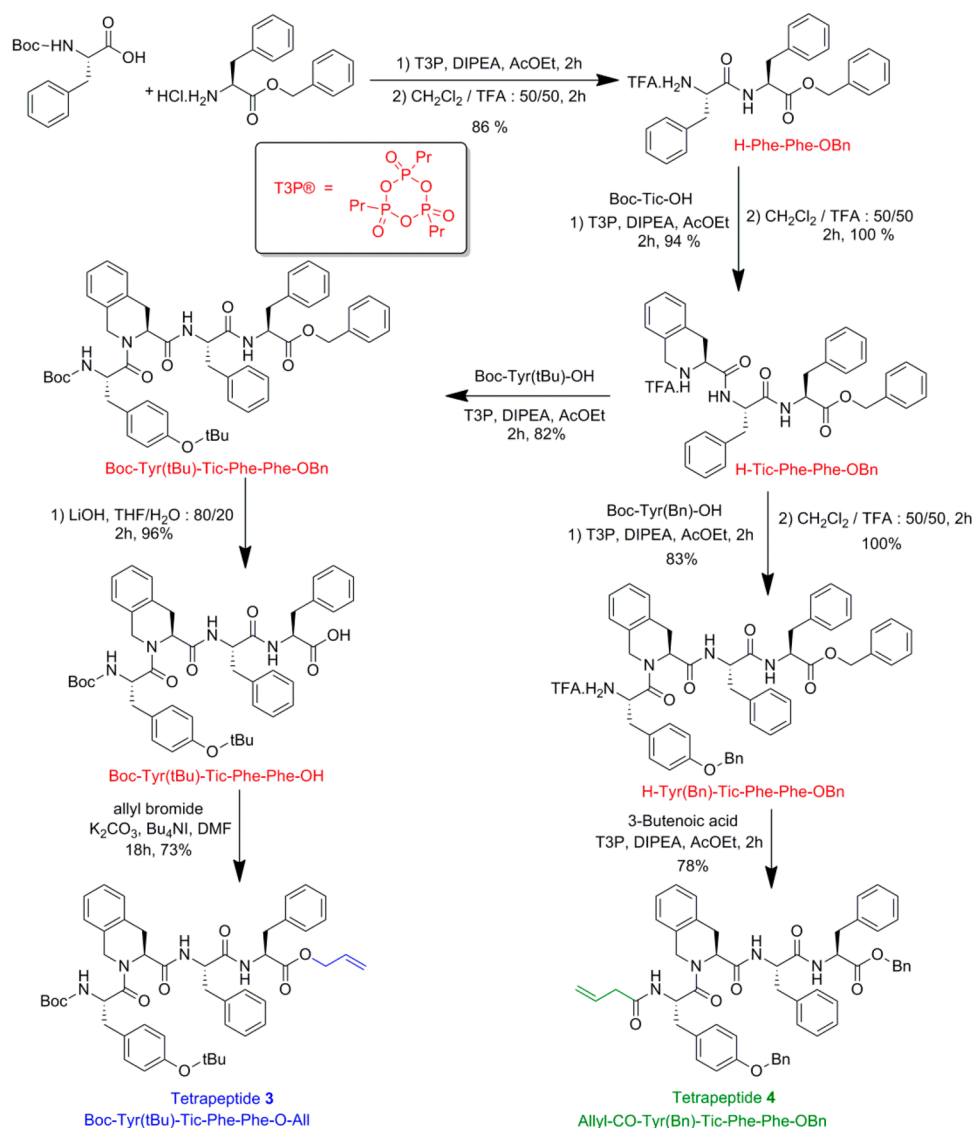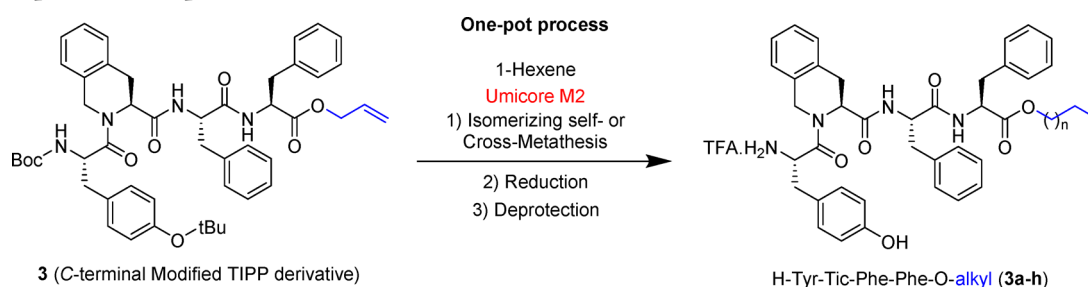

Hence, microwave irradiation was also used for the solid phase synthesis of the peptides in this work.

Solution-Phase Synthesis of Tetrapeptide 3 (Scheme 1). Boc-Phe-OH was condensed with HCl.H-Phe-OBn in the presence of DIPEA and T3P as a coupling reagent. After N-terminal Boc-deprotection with in a TFA/CH$_2$Cl$_2$ mixture, TFA-H-Phe-Phe-OBn was condensed with Boc-Tic-OH via a DIPEA/T3P coupling procedure (see Supporting Information). Subsequently, Boc-deprotection allowed the condensation of Boc-Tyr(tBu)-OH with H-Tic-Phe-Phe-OBn via the same DIPEA/T3P-mediated coupling procedure. After C-terminal benzyl hydrolysis with LiOH (THF/H$_2$O), allyl bromide was stirred with Boc-Tyr(tBu)-Tic-Phe-Phe-OH to present the final tetrapeptide 3, containing the C-terminal olefin (Boc-Tyr(tBu)-Tic-Phe-Phe-OAll). This compound was purified by preparative HPLC.

Solution-Phase Synthesis of Tetrapeptide 4 (Scheme 1). Using the common precursor H-Tic-Phe-Phe-OBn as the amine coupling partner, Boc-Tyr(Bn)-OH was linked to the N-terminus of this peptide. After N-terminal Boc deprotection, 3-butenoic acid was condensed with H-Tyr(Bn)Tic-Phe-Phe-OH

to give finally the corresponding tetrapeptide 4. This tetrapeptide 4 was again purified by preparative HPLC.

Microwave-Assisted Solid-Phase Synthesis of Tetrapeptides 5 and 6 Linked to Wang Resin. The short chain tetrapeptides 5 and 7 were synthesized manually by N^α-Fmoc methodology on Wang resin, preloaded with a Phe residue, under microwave irradiation (Biotage SP Wave, temperature was set at 75 °C). A 3-fold excess of the building blocks fmoc-protected amino acid (Fmoc-Xaa−OH), O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) and 6-fold excess N,N-diisopropylethylamine (DIEA) in DMF was added to the swollen resin. Under microwave irradiation, the mixture was shaken for 5 min with Fmoc-Phe-OH, 5 min with Fmoc-Tic-OH, and 5 min with Boc-Tyr(tBu)-OH or Boc-Tyr(All)-OH. The Fmoc protecting group was removed with 20% 4-methyl-piperidine in DMF for 20 min at room temperature without microwave irradiation. Next, the resin was filtered and respectively washed by vortexing for 1 min with DMF, MeOH, and CH$_2$Cl$_2$ to afford the tetrapeptides 5 and 7 linked to Wang resin. For structure confirmation, a micro-cleavage of the peptide from the resin followed by LC-MS

Table 1. One-pot solution-Phase Synthesis of *C*-terminal Modified TIPP Via the Tandem Isomerization/Cross-Metathesis/Reduction/Deprotection Sequences[a]

3 (*C*-terminal Modified TIPP derivative) → H-Tyr-Tic-Phe-Phe-O-alkyl (3a-h)

One-pot process
1-Hexene
Umicore M2
1) Isomerizing self- or Cross-Metathesis
2) Reduction
3) Deprotection

| *n* | peptide (3a−h) | rt[b] after HPLC purification (min) | yield[c] after HPLC purification (%) | clogP[d] | HRMS [M + H]+ | |
					calcd	found
1	H-Tyr-Tic-Phe-Phe-O-propyl (3a)	15.62	13	5.162	677.3334	677.3311
2	H-Tyr-Tic-Phe-Phe-O-butyl (3b)	16.18	13	5.691	691.3940	691.3502
3	H-Tyr-Tic-Phe-Phe-O-pentyl (3c)	16.86	9	6.220	705.3647	705.3643
4	H-Tyr-Tic-Phe-Phe-O-hexyl (3d)	17.52	11	6.749	719.3803	719.3604
5	H-Tyr-Tic-Phe-Phe-O-heptyl (3e)	17.78	12	7.278	733.3959	733.3970
6	H-Tyr-Tic-Phe-Phe-O-octyl (3f)	18.89	7	7.807	747.4116	747.4130
7	H-Tyr-Tic-Phe-Phe-O-nonyl (3g)	19.84	3	8.336	761.4272	761.4272
8[e]	H-Tyr-Tic-Phe-Phe-O-decyl (3h)	21.23	traces	8.865	775.3	775.4

[a]Reaction conditions: (1) 3 (0.1 mmol), 1-hexene (0.4 mmol), Umicore M2 (0.01 mmol); CH_2Cl_2 (3 mL), 24 h, 50 °C; (2) Umicore M2 (0.01 mmol), Et_3SiH (1 mmol), 48 h, 50 °C; (3) TFA/CH_2Cl_2:50/50, 2 h, room temperature. [b]Retention time was determined by HPLC (standard gradient) with UV detection at 215 nm. [c]Yields refer to isolated peptides. [d]Estimated by ChemBioOffice 2010. [e]The peptide was not isolated and the rt refer to the HPLC and the mass refer to the LCMS of the crude mixture.

analysis, confirmed that the desired supported peptides **5** and **7** were obtained with excellent purity.

Solid-Phase Synthesis of Tetrapeptide 7 Linked to Wang Resin. The linear solid supported tetrapeptide **7** was synthesized manually by N^α-Fmoc methodology on Wang resin, preloaded with a Phe residue, using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU)/*N*-methylmorpholine (NMM) as the coupling mixtures. A 3-fold excess of the building blocks (Fmoc-Phe-OH, Fmoc-Tic-OH, and Boc-Dmt(All)-OH] and activating agents were applied in the presence of 3 mL of NMM (0.4 M in DMF). Fmoc deprotections were carried out by treating the resin with 20% 4-methyl-piperidine in DMF. After completion of the coupling, the resin was filtered and respectively washed with DMF, MeOH, and CH_2Cl_2 to give the tetrapeptide **7** linked to Wang resin. A microcleavage and subsequent LC-MS analysis confirmed the presence of pure solid-supported peptide precursor.

Synthesis of Alkylated Tetrapeptides through Isomerization-Cross-Metathesis Reduction (ICMR). Having olefin-bearing tetrapeptide building blocks **3** to **7** in hand, the next step consisted of studying the tandem cross-metathesis-reduction reactions, to obtain the desired set of alkylated tetrapeptides. Toward this end, it was decided to first investigate the cross metathesis (CM) approach on the C-terminal allyl ester **3** as the peptide substrate with 1-hexene in the presence of Umicore M2 catalyst **1**, followed by reduction of double bonds by use of Et_3SiH in the presence of Umicore M2 via one-pot process (Table 1). The reaction was performed in a dried and sealed vial containing peptide in dry CH_2Cl_2, 1-hexene (4 equiv) and Umicore M2 catalyst **1** (0.1 equiv). The solution was heated at 50 °C in a sealed vial for 24 h. Next, additional Umicore M2 catalyst (0.1 equiv) and added Et_3SiH (10 equiv) resulted in quantitative reduction of the olefin at 50 °C in CH_2Cl_2 for 48 h. Final Boc and t-butyl deprotection of

the peptide was accomplished by treatment with TFA/CH_2Cl_2 50:50 for 2 h. The peptides were isolated by filtration and purified by preparative RP-HPLC on a Supelco Discovery BIO wide pore preparative C18 column in good overall yield. Surprisingly, this one-pot tandem reaction resulted in the formation of eight peptides **3a−h** (Table 1). To our delight, the compounds could be separated to high purity in a 30 to 100% CH_3CN in water gradient. The structure of the pure compounds was confirmed by high-resolution electrospray ionization (ESP) mass spectrometry. Although moderate yields are logically obtained for each compound, the sum of the isolated compounds represents 70%. (See Supporting Information for more details and HPLC chromatogram examples.) All results are summarized in Table 1.

Indeed, the isomerization/migration of 1-hexene is catalyzed by Umicore M2 complexes and leads to the thermodynamically more stable products: 2-hexene and 3-hexene, compounds which are of significant industrial interest.[11] The fast isomerization of 1-hexene to 2-hexene or 3-hexene is in accordance with previous observations described in literature.[11] In 1975, Porri et al. reported the first observation of a double bond isomerization/cross-metathesis process, after the observation of olefin mixture formation, with mixed iridium/silver systems, rather than the expected polyolefins by olefin polymerization.[12] Thereafter, Grubbs et al. demonstrated that the conversion of 1-octadecene into an olefin mixture with a broad chain length distribution can be achieved by using the same catalyst system.[13] Such isomerization reactions offer the possibility of forming multiple products in a single step.[14] More recently, Consorti and Dupont reported the formation of a mixture of olefins with up to 17 methylene units via the isomerizing metathesis of (*E*)-3-hexene with a combination of 0.5 mol % modified Hoveyda−Grubbs metathesis catalyst and 1 mol % ruthenium hydride isomerization catalyst in an ionic liquid.[15] Many Ru-hydrides are known to effect alkene isomerization in
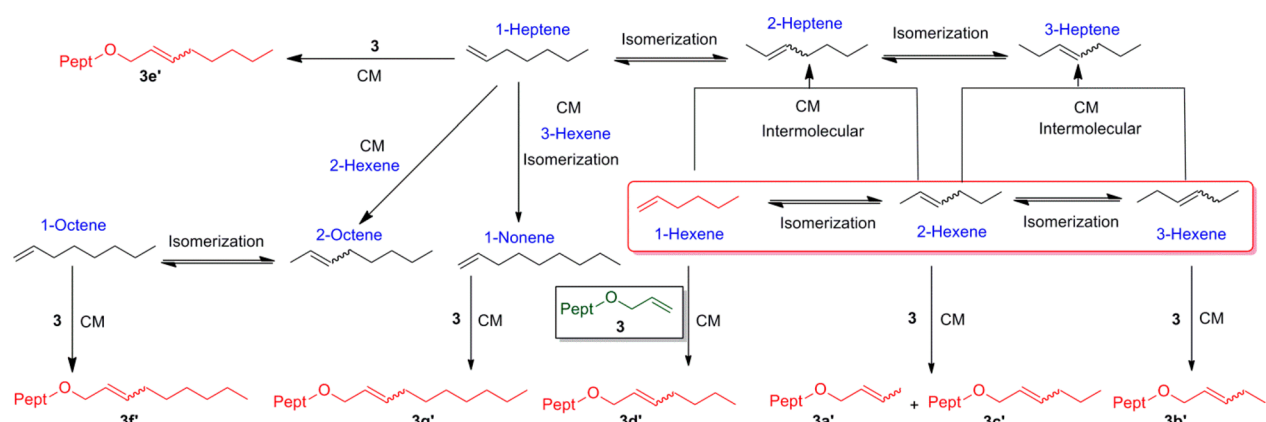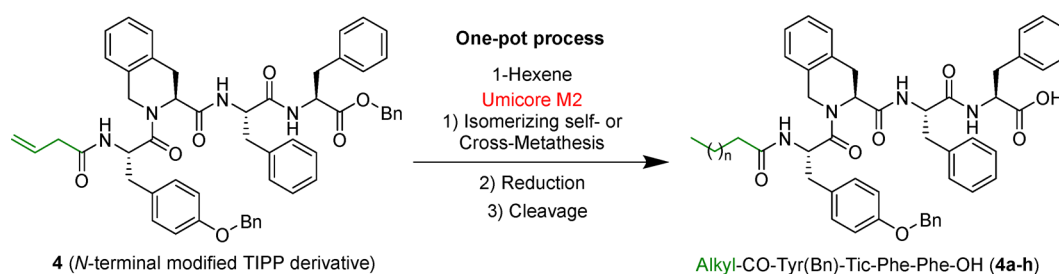
Figure 4. Proposed mechanism for isomerizing self-metathesis between the olefin-bearing peptide and the isomers of 1-hexene.

Table 2. One-Pot Solution-Phase Synthesis of N-Terminal-Modified TIPP via the Isomerization/Cross-Metathesis/Reduction Sequences[a]

n	peptide (4a–h)	rt[b] after HPLC purification (min)	yield[c] after HPLC purification (%)	clogP[d]	HRMS [M + H]+	
					calcd	found
1[e]	propyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4a**)	19.97	traces	7.357	795.3	795.4
2	butyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4b**)	20.45	17	7.886	809.3909	809.3922
3	pentyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4c**)	21.00	10	8.415	845.3883	845.3885
4	hexyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4d**)	21.58	12	8.944	837.4241	837.4222
5	heptyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4e**)	22.12	9	9.473	851.4379	851.4378
6	octyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4f**)	22.61	9	10.002	887.4330	877.4354
7	nonyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4g**)	23.22	4	10.531	901.4492	901.4510
8	decyl-CO-Tyr(Bn)-Tic-Phe-Phe-OH (**4h**)	23.57	3	11.060	893.4896	893.4848

[a]Reaction conditions: (1) **4** (0.1 mmol), 1-hexene (0.4 mmol), Umicore M2 (0.01 mmol); CH2Cl2 (3 mL), 24 h, 50 °C; (2) Umicore M2 (0.01 mmol), Et3SiH (1 mmol), 48 h, 50 °C; (3) Pd/C/H2, MeOH, atmospheric pressure, 2 h, room temperature. [b]Retention time was determined by HPLC (standard gradient) with UV detection at 215 nm. [c]Yields refer to isolated pure peptides. [d]Estimated by ChemBioOffice 2010. [e]The peptide was not isolated and the rt refer to the HPLC and the mass refer to the LCMS of the crude mixture.
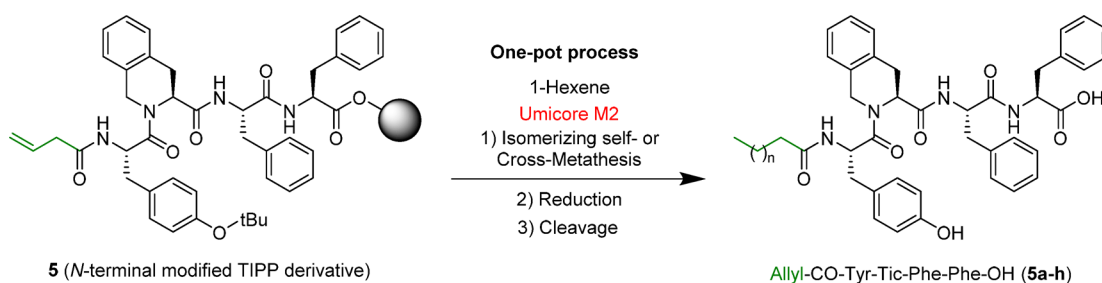
general, as demonstrated for the second generation Grubbs catalyst **2**.[16] The double bond migration is thought to be the result of the presence of metal-hydride intermediates formed in solution under metathesis condition.[17]

The CM reactions are more complex due to competition between the desired CM reaction, undesired self-metathesis (which leads to homodimers), and CM consuming the isomers formed in the solution. According to the literature,[18] by-products formed by alkene-isomerization (AI) and subsequent self-metathesis can be formed in situ. In our case, isomerization and self-metathesis products of 1-hexene underwent CM with olefin-derivatized peptide **3** to afford the unexpected peptides **3a′−g′** (prime numbering corresponds to unsaturated and intermediate peptide analogues). The chain lengths of alkene isomerization/CM products observed by LC-MS were generally 1, 2, 3, or 4 CH2 units longer or shorter, as compared to the nonisomerized olefin CM product **3d′** (Figure 4). It cannot be excluded that under the reactions conditions, also isomerization of the alkenes in **3a′−g′**, with potentially further cross

metathesis, occurs. The fact that no chains longer than in **3g′** were observed, indicates that such an isomerization−metathesis pathway is not occurring to an appreciable extent.

Additionally, we now report a new method for in situ olefin reduction under mild "hydrogen-free" (i.e., no added H2) conditions, using Et3SiH and the ruthenium-based olefin metathesis catalysts, through a one-pot process ICMR. More recently, an efficient solution and SPOS reduction of α,β-unsaturated alkenes was published by Mata and co-workers employing Grubbs' II catalyst in a nonmetathetic role and Et3SiH under microwave irradiation conditions.[19] However, our procedure is interesting as it shows that microwave heating is not always necessary to reach high conversions and excellent yields. Moreover, in this study the methodology is applied on peptide sequences that are of higher molecular complexity when compared to previous substrates.

To expand the reaction scope and to study the feasibility of the one pot isomerization self-metathesis/cross-metathesis/reduction sequence in solution (Table 1), we decided to repeat

Table 3. One-Pot Solid-Phase Synthesis of N-Terminal-Modified TIPP Via the Tandem Isomerization/Cross-Metathesis/Reduction/Cleavage Reactions[a]

5 (*N*-terminal modified TIPP derivative) → Allyl-CO-Tyr-Tic-Phe-Phe-OH (5a-h)

One-pot process
1-Hexene
Umicore M2
1) Isomerizing self- or Cross-Metathesis
2) Reduction
3) Cleavage

n	peptide (5a−h)	rt[b] after HPLC purification (min)	yield[c] after HPLC purification (%)	clogP[d]	HRMS [M + H]+ calcd	found
1	propyl-CO-Tyr-Tic-Phe-Phe-OH (5a)	16.10	20	5.003	705.3282	705.3298
2	butyl-CO-Tyr-Tic-Phe-Phe-OH (5b)	17.09	16	5.532	719.3439	719.3406
3	pentyl-CO-Tyr-Tic-Phe-Phe-OH (5c)	17.39	12	6.061	733.3596	733.3608
4	hexyl-CO-Tyr-Tic-Phe-Phe-OH (5d)	18.08	11	6.590	747.3752	747.3763
5	heptyl-CO-Tyr-Tic-Phe-Phe-OH (5e)	19.10	8	7.119	761.3909	761.3925
6	octyl-CO-Tyr-Tic-Phe-Phe-OH (5f)	18.87	5	7.648	775.4066	775.4070
7	Nonyl-CO-Tyr-Tic-Phe-Phe-OH (5g)	20.66	3	8.177	789.4257	789.4222
8[e]	Decyl-CO-Tyr-Tic-Phe-Phe-OH (5h)	21.21	traces	8.706	803.4	803.3

[a]Reaction conditions: (1) 5 (0.1 mmol), 1-hexene (0.4 mmol), Umicore M2 (0.01 mmol); CH$_2$Cl$_2$ (3 mL), 24 h, 50 °C; (b) Umicore M2 (0.01 mmol), Et$_3$SiH (1 mmol), 48 h, 50 °C; (c) TFA/CH$_2$Cl$_2$ = 50/50, 2 h, room temperature. [b]Retention time was determined by HPLC (standard gradient) with UV detection at 215 nm. [c]Yields refer to isolated pure peptides. [d]Estimated by ChemBioOffice 2010. [e]The peptide was not isolated and the rt refer to the HPLC and the mass refer to the LCMS of the crude mixture.

Table 4. One-Pot Solid-Phase Synthesis of Side-Chain-Modified TIPP Via the Tandem Isomerization/Cross-Metathesis/Reduction/Cleavage Reactions[a]
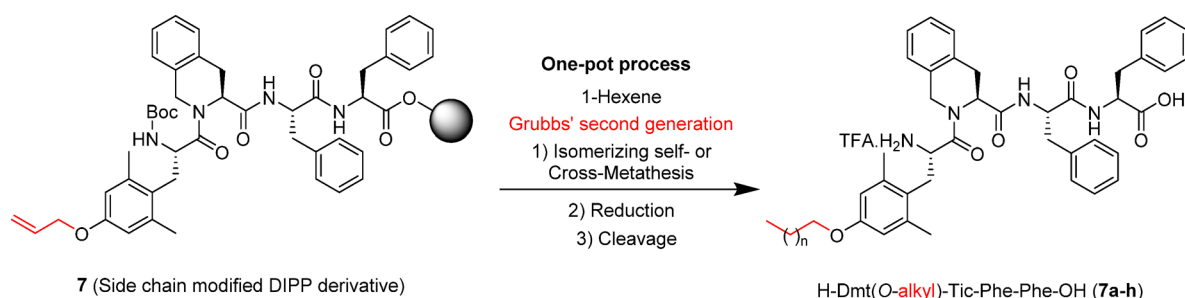

6 (Side chain modified TIPP derivative) → H-Tyr(*O*-alkyl)-Tic-Phe-Phe-OH (6a-h)

One-pot process
1-Hexene
Umicore M2
1) Isomerizing self- or Cross-Metathesis
3) Reduction
4) Cleavage
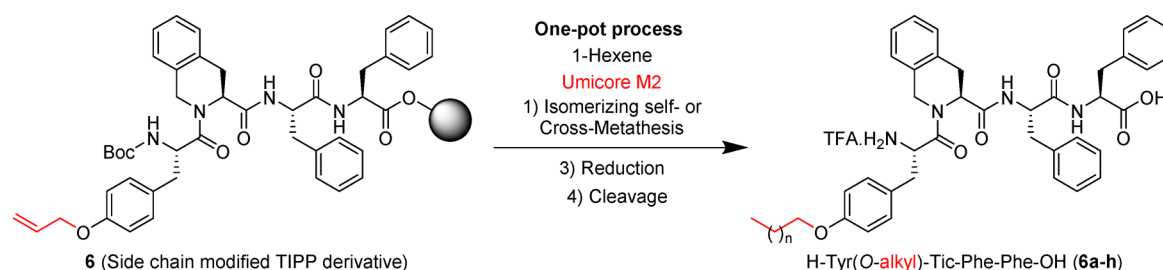
n	peptide (6a−h)	rt[b] after HPLC purification (min)	yield[c] after HPLC purification (%)	clogP[d]	HRMS [M + H]+ calcd	found
1	H-Tyr(*O*-propyl)-Tic-Phe-Phe-OH (6a)	15.41	18	3.359	677.3334	677.3331
2	H-Tyr(*O*-butyl)-Tic-Phe-Phe-OH (6b)	16.05	14	3.888	691.3940	691.3466
3	H-Tyr(*O*-pentyl)-Tic-Phe-Phe-OH (6c)	16.70	15	4.417	705.3647	705.3622
4	H-Tyr(*O*-hexyl)-Tic-Phe-Phe-OH (6d)	17.45	9	4.946	719.3803	719.3822
5	H-Tyr(*O*-heptyl)-Tic-Phe-Phe-OH (6e)	18.21	7	5.475	733.3959	733.3943
6	H-Tyr(*O*-octyl)-Tic-Phe-Phe-OH (6f)	18.99	5	6.004	747.4116	747.4127
7[e]	H-Tyr(O-nonyl)-Tic-Phe-Phe-OH (6g)	9.84	5	6.533	761.4272	761.4295
8[e]	H-Tyr(O-decyl)-Tic-Phe-Phe-OH (6h)	10.88	3	7.062	775.4421	775.4429

[a]Reaction conditions: (1) 6 (0.1 mmol), 1-hexene (0.4 mmol), Umicore M2 (0.01 mmol); CH$_2$Cl$_2$ (3 mL), 24 h, 50 °C; (2) Umicore M2 (0.01 mmol), Et$_3$SiH (1 mmol), 48 h, 50 °C. 3) TFA/CH$_2$Cl$_2$ = 50/50, 2 h, room temperature. [b]Retention time was determined by HPLC (standard gradient) with UV detection at 215 nm. [c]Yields refer to isolated pure peptides. [d]Estimated by ChemBioOffice 2010. [e]The rt refer to the HPLC (60−100% of CH$_3$CN as gradient).

the IMCR procedure for N-terminal-modified tetrapeptide 4 by application of the above-described reaction conditions. As expected, eight peptides were obtained (six of which could be isolated after prep-HPLC). Again a good global yield of 64% (taking into consideration the sum of all components) and high purity was observed after preparative RP-HPLC (see Supporting Information). The apparent low to moderate yields of the individual components are not considered as problematic

since our primary interest is the rapid synthesis of a variety of peptide derivatives for initial biological evaluation, rather than high individual yields, commonly aimed for in methodological studies. As a result of the reduction reaction and subsequent acidolysis, only the benzyl ester was removed, while the benzyl ether group remained on the peptide. This observation could potentially be of interest as one derivatization handle remains
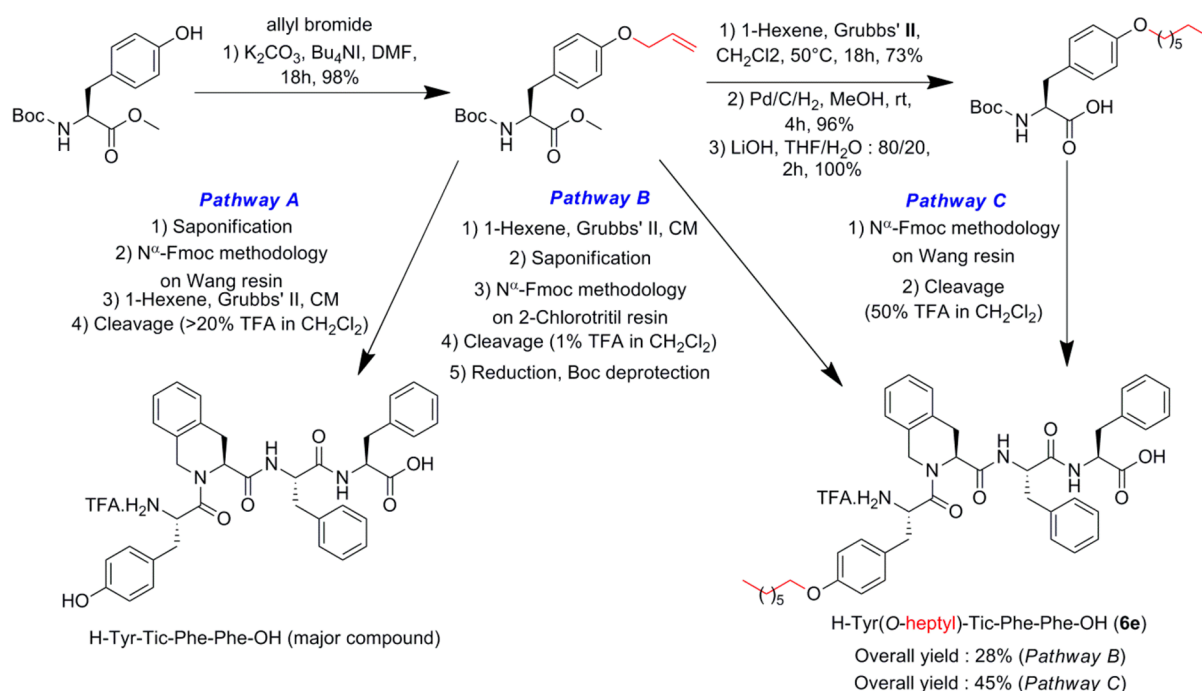
Table 5. One-Pot Solid-Phase Synthesis of Side-Chain-Modified DIPP Via the Tandem Isomerization/Cross-Metathesis/Reduction/Cleavage Reactions[a]

7 (Side chain modified DIPP derivative)　　　　H-Dmt(O-alkyl)-Tic-Phe-Phe-OH (**7a-h**)

One-pot process
1-Hexene
Grubbs' second generation
1) Isomerizing self- or Cross-Metathesis
2) Reduction
3) Cleavage

n	peptide (**7a–h**)	rt[b] after HPLC purification (min)	yield[c] after HPLC purification (%)	clogP[d]	HRMS[M + H]$^+$ found	HRMS[M + H]$^+$ calcd
1	H-Dmt(OHJ-Tic-Phe-Phe-OH (**7a**)	13.74	17	2.613	663.3177	663.3166
2	H-Dmt(O-propyl)-Tic-Phe-Phe-OH (**7b**)	15.04	12	4.257	705.3647	705.3657
3	H-Dmt(O-butyl)-Tic-Phe-Phe-OH (**7c**)	16.43	11	4.786	719.3803	719.3795
4	H-Dmt(O-pentyl)-Tic-Phe-Phe-OH (**7d**)	17.11	9	5.315	733.3959	733.3958
5	H-Dmt(O-hexyl)-Tic-Phe-Phe-OH (**7e**)	17.78	9	5.844	747.4116	747.4092
6	H-Dmt(O-heptyl)-Tic-Phe-Phe-OH (**7f**)	18.49	7	6.373	761.4235	761.4235
7	H-Dmt(O-octyl)-Tic-Phe-Phe-OH (**7g**)	19.22	4	6.902	775.4429	775.4414
8[e]	H-Dmt(O-nonyl)-Tic-Phe-Phe-OH (**7h**)	20.00	traces	7.431	789.5	789.6
9[e]	H-Dmt(O-decyl)-Tic-Phe-Phe-OH (**7i**)	21.08	traces	7.960	803.5	803.6

[a]Reaction conditions: (1) **7** (0.1 mmol), 1-hexene (0.4 mmol), Grubbs' second generation (0.01 mmol); CH$_2$Cl$_2$ (3 mL), 24 h, 50 °C; (2) Grubbs' second generation (0.01 mmol), Et$_3$SiH (1 mmol), 48 h, 50 °C; (3) TFA/CH$_2$Cl$_2$ = 50/50, 2 h, room temperature. [b]Retention time was determined by HPLC (standard gradient) with UV detection at 215 nm. [c]Yields refer to isolated pure peptides. [d]Estimated by ChemBioOffice 2010. [e]The peptide was not isolated and the rt refer to the HPLC and the mass refer to the LCMS of the crude mixture.

Scheme 2. Preparation of Tetrapeptide H-Tyr(O-heptyl)-Tic-Phe-Phe-OH (6e) Under Classical Cross-Metathesis Reaction Conditions in a Roundbottom Flask

allyl bromide
1) K$_2$CO$_3$, Bu$_4$NI, DMF, 18h, 98%

1) 1-Hexene, Grubbs' II, CH$_2$Cl$_2$, 50°C, 18h, 73%
2) Pd/C/H$_2$, MeOH, rt, 4h, 96%
3) LiOH, THF/H$_2$O : 80/20, 2h, 100%

Pathway A
1) Saponification
2) N$^\alpha$-Fmoc methodology on Wang resin
3) 1-Hexene, Grubbs' II, CM
4) Cleavage (>20% TFA in CH$_2$Cl$_2$)

Pathway B
1) 1-Hexene, Grubbs' II, CM
2) Saponification
3) N$^\alpha$-Fmoc methodology on 2-Chlorotritil resin
4) Cleavage (1% TFA in CH$_2$Cl$_2$)
5) Reduction, Boc deprotection

Pathway C
1) N$^\alpha$-Fmoc methodology on Wang resin
2) Cleavage (50% TFA in CH$_2$Cl$_2$)

H-Tyr-Tic-Phe-Phe-OH (major compound)

H-Tyr(O-heptyl)-Tic-Phe-Phe-OH (**6e**)
Overall yield : 28% (*Pathway B*)
Overall yield : 45% (*Pathway C*)

on the peptide analogue. Detailed results are collected in Table 2.

In an attempt to broaden the applicability of the ICMR conditions, compatibility with solid supports was verified. Generally, olefin cross metathesis on solid phase has several potential advantages as compared to its solution phase counterpart. Under SPOS conditions, the immobilization of

one of the olefin substrates makes its homodimerization less favored due to site isolation (pseudodilution), while the olefin that remains in solution can be added in excess to push the reaction to total conversion. The dimer or byproducts can easily be eliminated by filtration. Additionally, solid-phase organic synthesis permits automation and parallel synthesis,

opening a gateway for the rapid generation of combinatorial libraries.[20]

Exposure of tetrapeptides **5** (N-terminal-modified TIPP) and **6** (side chain modified TIPP), which are still linked to Wang resin, to the one-pot tandem ICMR conditions, afforded directly the desired and expected products **5a–h** and **6a–h** with overall yields of 75% and 76%, respectively. Interestingly, in the case of the resin-bound tetrapeptide **5**, the overall yield was 11% higher than was observed in the reaction performed with the corresponding peptide (**4**) in solution.

Furthermore, the *N*-propyl-containing peptide **5a** was the most abundant component, whereas it was produced in traces only in the solution phase synthesis carried out with **4**. The peptides were obtained in moderate yields and were purified by RP-HPLC. The results are summarized in Tables 3 and 4. This method is of value since only a few protocols (based on diimide reduction) of double bonds on solid phase are available.[21] In addition, the diimide protocol appeared to be potentially problematic when attempting reproduction in solution.[19] It can be noted that cleavage of the peptides from the Wang resin, directly after the cross-metathesis reaction on **6**, and before reduction, resulted only in *O*-dealkylated peptide, due to the well-known acid sensitivity of *O*-allyl type protecting groups. This is an indirect argument for the fact that double bond isomerization (such as discussed for **3a′–g′**, Figure 4) in the final compounds is not, or in a very minor amount, occurring.

Finally, to show that the ICMR protocol is not restricted to the Umicore M2 catalyst **1**, we switched to the more commonly used Grubbs' II **2** ruthenium catalyst. The one-pot tandem ICMR reactions of Wang resin-linked tetrapeptides of type **7** (i.e., side chain modified DIPP) was accomplished by use of catalyst **2**, to give the expected eight tetrapeptides (7 of which isolated by purification, see Table 5) in a global yield 52%. In this case the conversion was not as complete, compared to the equivalent ICMR conditions using Umicore M2 catalyst (Table 5 versus Table 4). The observed phenol-deprotected tetrapeptide **7a** was isolated in 17% yields because of the acid sensitivity of the *O*-allyl-type protecting group presented in building block **7**.

To confirm the actual identity of all homologues obtained through the ICMR method, tetrapeptides **6a–h** were prepared individually in solution or on solid-phase (Scheme 2). At this point, it should be noted that the cross-metathesis under classical heating conditions (i.e., with round-bottom flask and cooler), affords only a single peptide (see Supporting Information for more details). This in contrast to the described conditions in a sealed vial (vide supra), for which a mixture of derivatives are observed and isolated. As depicted in Scheme 2, the use of Wang resin turned out to be problematic when attempting the isolation of the alkenyl-derived peptide. During the acidic cleavage from the solid support (pathway A) removal of the alkenyl substituent was observed. Tetrapeptide **6e** was however prepared in good yield via two pathways: (B) using the 2-chlorotrityl resin as solid support (milder acidic conditions are required for peptide cleavage), followed by double bound hydrogenation and subsequent removal of the Boc protecting group and (C) performing the CMR reaction on the Boc-Tyr(All)-OMe and alkenyl reduction before the peptide couplings. The peptide products that were obtained in this way were purified by preparative RP-HPLC and subsequently coinjected in HPLC with the purified ICMR products. As such, the structures of **6a–h** were confirmed by identical retention times.

Of the 40 lipophilic tetrapeptides, 32 were obtained with purity of ≥95% in 3−13 mg quantity. The calculated clogP (3.359−11.060) values of the peptides in this library matched very well with those obtained for previously reported bioactive opioid peptides.[1c−e,2c,22] The clogP values for our isolated lipophilic tetrapeptides **3a–f**, **5a–f**, **6a–f**, and **7a–f** (modified DIPP and TIPP derivatives) are situated between 3.359 and 7.807, which make them hydrophobic peptide candidates for further membrane transport and, in this case, opioid bioactivity studies.

In summary, we were able to establish a new and efficient fast protocol to generate wide sets of lipophilic tetrapeptide TIPP and DIPP derivatives by one-pot tandem isomerization/cross-metathesis/reduction reactions (ICMR) on solid phase and/or in solution. The ICMR reactions were achieved by application of Grubbs' second-generation or Umicore M2 precatalyst to the olefin cross-metathesis of *N*-terminally, *C*-terminally or side chain allylated tetrapeptides, followed by reduction of the alkenes in the presence of triethylsilane on a solid supports or/and in solution. The solid phase experimental procedure did not require any air exclusion precautions. The desired products were isolated in good global yields and with excellent purity, as determined by RP-HPLC and LC-MS. The biological activity and the potential of the new lipophilic tetrapeptides are under investigation and will be reported in due course.

■ EXPERIMENTAL PROCEDURES

General Procedure for the Direct Solid-Phase Synthesis of a Series of Lipophilic Tetrapeptides (7a–h) Via the Cascade Coupling/Isomerization/Cross-Metathesis/Reduction/Cleavage Reactions. The linear tetrapeptides were synthesized manually by *Nα*-Fmoc methodology on Phe-Wang resin (0.1 mmol scale) using *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU)/*N*-methylmorpholine (NMM) as the coupling reagents/mixtures. A 3-fold excess of the building blocks [Fmoc-Phe-OH, Fmoc-Tic-OH, and Boc-Dmt(*O*All)-OH] and activating agents was applied in the presence of 3 mL of NMM (0.4 M in DMF). Fmoc-AA-OH and NMM in DMF were added to the swollen solid support, and the reaction mixture was shaken for 3 h. The resin was washed three times with DMF, three times with *i*-PrOH and three times with CH$_2$Cl$_2$. Completion of the coupling was tested by means of the Kaiser or chloranil test. Coupling of Boc-Dmt(*O*All)-OH was repeated twice to give a negative chloranil test. The next amino-acid was consecutively coupled using the procedure described above. Fmoc deprotections were carried out by treating the resin twice (5 and 30 min) with 20% 4-methyl-piperidine in DMF. After completion of the coupling, the resin was transferred into a sealed dry vial containing 3 mL of dry CH$_2$Cl$_2$ then, 1-hexene (0.4 mmol) and Grubbs' second generation catalyst **2** (0.01 mmol) were added consecutively. The solution was heated at 50 °C in a sealed vial for 24 h. Rh(I)-catalyzed homogeneous hydrogenation using Grubbs catalyst (0.01 mmol) in the presence of Et$_3$SiH (1 mmol) effected quantitative reduction of the resin-attached alkene at 50 °C in CH$_2$Cl$_2$ for 48 h. The resin was washed three times with DMF, three times with *i*-PrOH, and three times with CH$_2$Cl$_2$. Final cleavage of the peptide from the resin as well as the Boc side chain protection group removal was accomplished by treatment with TFA/CH$_2$Cl$_2$/Et$_3$SiH/H$_2$O 60:35:2.5/2.5 for 2 h. The peptides were isolated by filtration and purified by RP-HPLC (30% to 100% of CH$_3$CN as gradient) on a Supelco Discovery BIO wide pore preparative C18 column in good

overall yield and was >95% pure as determined by analytical RP-HPLC and. The structure of pure compounds was confirmed by high-resolution electrospray ionization (ESP) mass spectrometry. This reaction conducted to the formation of eight peptides: H-Dmt-Tic-Phe-Phe-OH (17%, 12.9 mg), H-Dmt(propyl)-Tic-Phe-Phe-OH (12%, 9.6 mg), H-Dmt(butyl)-Tic-Phe-Phe-OH (11%, 10 mg), H-Dmt(pentyl)-Tic-Phe-Phe-OH (9%, 7.5 mg), H-Dmt(hexyl)-Tic-Phe-Phe-OH (9%, 7.6 mg), H-Dmt(heptyl)-Tic-Phe-Phe-OH (7%, 6 mg), H-Dmt-(octyl)-Tic-Phe-Phe-OH (4%, 3.5 mg), H-Dmt(nonyl)-Tic-Phe-Phe-OH (traces), H-Dmt(decyl)-Tic-Phe-Phe-OH (traces).

Peptide Characterization. *H-Dmt-Tic-Phe-Phe-OH (7a).* HPLC (standard gradient): t_{ret} = 13.74 min. ESI-HRMS [M + H$^+$]: m/z = 663.3166 (calcd for C$_{39}$H$_{42}$H$^+$N$_4$O$_6$ 663.3177).

H-Dmt(propyl)-Tic-Phe-Phe-OH (7b). HPLC (standard gradient): t_{ret} = 15.04 min. TLC R_f (EBAW), 0.79. ESI-HRMS [M + H$^+$]: m/z = 705.3657 (calcd for C$_{42}$H$_{48}$H$^+$N$_4$O$_6$ 705.3647).

H-Dmt(butyl)-Tic-Phe-Phe-OH (7c). HPLC (standard gradient): t_{ret} = 16.43 min. TLC R_f (EBAW), 0.80. ESI-HRMS [M + H$^+$]: m/z = 719.3795 (calcd for C$_{43}$H$_{50}$H$^+$N$_4$O$_6$ 719.3803).

H-Dmt(pentyl)-Tic-Phe-Phe-OH (7d). HPLC (standard gradient): t_{ret} = 17.11 min. TLC R_f (EBAW), 0.81. ESI-HRMS [M + H$^+$]: m/z = 733.3958 (calcd for C$_{44}$H$_{52}$H$^+$N$_4$O$_6$ 733.3959).

H-Dmt(hexyl)-Tic-Phe-Phe-OH (7e). HPLC (standard gradient): t_{ret} = 17.78 min. TLC R_f (EBAW), 0.82. ESI-HRMS [M + H$^+$]: m/z = 747.4092 (calcd for C$_{45}$H$_{54}$H$^+$N$_4$O$_6$ 747.4116).

H-Dmt(heptyl)-Tic-Phe-Phe-OH (7f). HPLC (standard gradient): t_{ret} = 18.49 min. TLC R_f (EBAW), 0.83. ESI-HRMS [M + H$^+$]: m/z = 761.4235 (calcd for C$_{46}$H$_{56}$H$^+$N$_4$O$_6$ 761.4272).

H-Dmt(octyl)-Tic-Phe-Phe-OH (7g). HPLC (standard gradient): t_{ret} = 19.22 min. TLC R_f (EBAW), 0.84. ESI-HRMS [M + H$^+$]: m/z = 775.4414 (calcd for C$_{47}$H$_{58}$H$^+$N$_4$O$_6$ 775.4429).

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors
*E-mail: mouhamad.jida@vub.ac.be.
*E-mail: sballet@vub.ac.be.

Author Contributions

M.J., C.B., and S.B. synthesized all peptide analogues. In addition, S.B., D.T., and P.W.S. were in charge of the coordination and the writing of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

ABBREVIATIONS

DIPEA, *N,N*-diisopropylethylamine; DMF, *N,N*-dimethylformamide; Dmt, 2′,6′-dimethyl-(*S*)-tyrosine; TBTU, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate; NMM, *N*-methylmorpholine; BBB, blood−brain barrier; ICMR, isomerization/cross-metathesis/reduction

REFERENCES

(1) For selected examples, see (a) Vandormael, B.; Fourla, D.-D.; Gramowski-Voß, A.; Kosson, P.; Weiss, D. G.; Schröder, O.H-U.; Lipkowski, A. W.; Georgoussi, Z.; Tourwé, D. Superpotent [Dmt1] dermorphin tetrapeptides containing the 4-aminotetrahydro-2-benza-zepin-3-one scaffold with mixed μ/δ opioid receptor agonistic properties. *J. Med. Chem.* **2011**, *54*, 7848−7859. (b) Ballet, S.; Feytens, D.; Buysse, K.; Chung, N. N.; Lemieux, C.; Tumati, S.; Keresztes, A.; Van Duppen, J.; Lai, J.; Varga, E.; Porreca, F.; Schiller, P. W.; Vanden Broeck, J.; Tourwé, D. Design of novel neurokinin 1 receptor antagonists based on conformationally constrained aromatic amino acids and discovery of a potent chimeric opioid agonist-neurokinin 1 receptor antagonist. *J. Med. Chem.* **2011**, *54*, 2467−2476. (c) Ballet, S.; Frycia, A.; Piron, J.; Chung, N. N.; Schiller, P. W.; Kosson, P.; Lipkowski, A. W.; Tourwé, D. Synthesis and biological evaluation of constrained analogues of the opioid peptide H-Tyr-D-Ala-Phe-Gly-NH$_2$ using 4-amino-2-benzazepin-3-one scaffold. *J. Peptide Res.* **2005**, *66*, 222−230. (d) Ballet, S.; Feytens, D.; De Wachter, R.; De Vlaeminck, M.; Marczak, E. D.; Salvadori, S.; de Graaf, C.; Rognan, D.; Negri, L.; Lattanzi, R.; Lazarus, L. H.; Tourwé, D.; Balboni, G. Conformationally constrained opioid ligands: The Dmt-Aba and Dmt-Aia versus Dmt-Tic scaffold. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 433−437. (e) Guillemyn, K.; Kleczkowska, P.; Novoa, A.; Vandormael, B.; Van den Eynde, I.; Kosson, P.; Asim, M. F.; Schiller, P. W.; Spetea, M.; Lipkowski, A. W.; Tourwé, D.; Ballet, S. In vivo antinociception of potent mu opioid agonist tetrapeptide analogues and comparison with a compact opioid agonist−neurokinin 1 receptor antagonist chimera. *Molecular Brain* **2012**, 5:4. (f) Schiller, P. W. Bi- or multifunctional opioid peptide drugs. *Life Sci.* **2010**, *86*, 598−603.

(2) (a) Schiller, P. W.; Nguyen, TM-D; Weltrowska, G.; Wilkes, B. C.; Marsden, B. J.; Lemieux, C.; Chung, N. N. Differential stereochemical requirements of μ vs. δ opioid receptors for ligand binding and signal transduction: Development of a class of potent and highly δ-selective peptide antagonists. *Proc. Natl. Acad. Sci. U. S. A* **1992**, *89*, 11871−11875. (b) Schiller, P. W.; Fundytus, M. E.; Merovitz, L.; Weltrowska, G.; Nguyen, T. M.-D.; Lemieux, C.; Chung, N. N.; Coderre, T. J. The opioid μ agonist/δ antagonist DIPP-NH$_2$[Ψ] produces a potent analgesic effect, no physical dependence, and less tolerance than morphine in rats. *J. Med. Chem.* **1999**, *42* (18), 3520−3526. (c) Weltrowska, G.; Nguyen, T. M.; Chung, N. N.; Wilkes, B. C.; Schiller, P. W. N-terminal guanidinylation of TIPP (Tyr-Tic-Phe-Phe) peptides results in major changes of the opioid activity profile. *Bioorg. Med. Chem. Lett.* **2013**, *18*, 5082−5083.

(3) (a) Balboni, G.; Guerrini, R.; Salvadori, S.; Bianchi, C.; Rizzi, D.; Bryant, S. D.; Lazarus, L. H. Evaluation of the Dmt-Tic pharmacophore: Conversion of a potent δ-opioid receptor antagonist into a potent δ-agonist and ligands with mixed properties. *J. Med. Chem.* **2002**, *45*, 713−720.

(4) (a) Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-based heterocyclic carbene-coordinated olefin metathesis catalysts. *Chem. Rev.* **2010**, *110*, 1746−1787. (b) Connon, S. J.; Blechert, S. Recent developments in olefin cross-metathesis. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (c) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. Applications of olefin cross metathesis to commercial products. *Adv. Synth. Catal.* **2002**, *344*, 728−735. (d) Lin, Y. A.; Boutureira, O.; Lercher, L.; Bhushan, B.; Paton, R. S.; Davis, B. G. Rapid cross-metathesis for reversible protein modifications via chemical access to Se-allyl-selenocysteine in Proteins. *J. Am. Chem. Soc.* **2013**, *135*, 12156−12159.

(5) (a) Lehman, S. E.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. Olefin isomerization promoted by olefin metathesis catalysts. *Inorg. Chim. Acta* **2003**, *345*, 190−198. (b) Dragutan, I.; Dragutan, V.; Demonceau, A. Targeted drugs by olefin metathesis: piperidine-based iminosugars. *RSC Adv.* **2012**, *2*, 719−736 and references therein..

(6) (a) Bantreil, X.; Schmid, T. E.; Randall, R. A. M.; Slawin, A. M. Z.; Cazin, C. S. J. Mixed N-heterocyclic carbene/phosphite ruthenium complexes: towards a new generation of olefin metathesis catalysts. *Chem. Commun.* **2010**, *46*, 7115−7117. (b) Urbina-Blanco, C. A.; Manzini, S.; Gomes, J. P.; Doppiu, A.; Nolan, S. P. Simple synthetic routes to ruthenium−indenylidene olefin metathesis catalysts. *Chem. Commun.* **2011**, *47*, 5022−5024.

(7) (a) Basavaprabhu; Vishwanatha, T. M.; Panguluri, N. R.; Sureshbabu, V. V. Propanephosphonic acid anhydride (T3P)—A benign reagent for diverse applications inclusive of large-scale synthesis. *Synthesis* **2013**, *45*, 1569−1601. (b) Jida, M.; Deprez, B. Friedländer synthesis of polysubstituted quinolines and naphthyridines promoted by propylphosphonic anhydride (T3P) under mild conditions. *New J. Chem.* **2012**, *36*, 869−873.

(8) Barrett, A. G. M.; Hennessy, A. J.; Vezouet, R. L.; Procopiou, P. A.; Searle, P. W.; Stefaniak, S.; Upton, R. J.; White, A. J. P.; Williams, D. J. Synthesis of diverse macrocyclic peptidomimetics utilizing ring-closing metathesis and solid-phase synthesis. *J. Org. Chem.* **2004**, *69*, 1028−1037.

(9) (a) Schnölzer, M.; Alewood, P.; Jones, A.; Alewood, D.; Kent, S. B. H. In situ neutralization in boc-chemistry solid phase peptide synthesis. *Int. J. Pept. Prot. Res.* **2009**, *40*, 180−193. (b) King, D. S.; Fields, C. G.; Fields, G. B. A cleavage method which minimizes side reactions following fmoc solid phase peptide synthesis. *Int. J. Pept. Prot. Res.* **2009**, *36*, 255−266 and references therein..

(10) (a) Pedersen, S. L.; Tofteng, A. P.; Malik, L.; Jensen, K. J. Microwave heating in solid-phase peptide synthesis. *Chem. Soc. Rev.* **2012**, *41*, 1826−1844. (b) Skwarczynski, M.; Hussein, W. M.; Liu, T.-Y.; Toth, I. Microwave-assisted synthesis of difficult sequence-containing peptide using the isopeptide method. *Org. Biomol. Chem.* **2013**, *11*, 2370−2376 and references therein..

(11) Mitkova, M.; Kurtev, K. Isomerization of 4-methyl-1-pentene and 1-hexene catalysed by macroporous ion exchange resin: A kinetic study. *J. Chin. Chem. Soc.* **2005**, *52*, 1185−1189.

(12) Porri, L.; Diversi, P.; Lucherini, A.; Rossi, R. Catalysts derived from ruthenium and iridium for the ring-opening polymerization of cycloolefins. *Makromol. Chem.* **1975**, *176*, 3121−3125.

(13) France, M. B.; Feldman, J.; Grubbs, R. H. An iridium-based catalyst system for metathesis/isomerization of acyclic olefins, including methyl-oleate. *J. Chem. Soc., Chem. Commun.* **1994**, 1307−1308.

(14) (a) Pillai, S. M.; Ravindranathan, M.; Sivaram, S. Dimerization of ethylene and propylene catalyzed by transition-metal complexes. *Chem. Rev.* **1986**, *86*, 353−399.

(15) Consorti, C. S.; Aydos, G. L. P.; Dupont, J. Tandem isomerisation−metathesis catalytic processes of linear olefins in ionic liquid biphasic system. *Chem. Commun.* **2010**, *46*, 9058−9060.

(16) Sanford, M. S. Synthetic and mechanistic investigations of ruthenium olefin metathesis catalysts. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 2001.

(17) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. New tandem catalysis: Preparation of cyclic enol ethers through a ruthenium-catalyzed ring-closing metathesis−olefin isomerization sequence. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (b) Hong, S. H.; Day, M. W.; Grubbs, R. H. Decomposition of a key intermediate in ruthenium-catalyzed olefin metathesis reactions. *J. Am. Chem. Soc.* **2004**, *126*, 7414−7415.

(18) Schwab, P.; Grubbs, R. H.; Ziller, J. W. Synthesis and applications of RuCl$_2$(=CHR′)(PR(3))(2): The influence of the alkylidene moiety on metathesis activity. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(19) Poeylaut-Palena, A. A.; Testero, S. A.; Mata, E. G. The non-metathetic role of Grubbs' carbene complexes: from hydrogen-free reduction of α,β-unsaturated alkenes to solid-supported sequential cross-metathesis/reduction. *Chem. Commun.* **2011**, *47*, 1565−1567.

(20) (a) Edwards, P. J.; Morrell, A. I. Solid-phase compound library synthesis in drug design and development. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 594−605. (b) Dolle, R. E.; Bourdonnec, B. L.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Thomas, C. J.; Zhang, W. Comprehensive survey of chemical libraries for drug discovery and chemical biology: 2009. *J. Comb. Chem.* **2010**, *12*, 765−806 and references therein..

(21) (a) Lacombe, P.; Castagner, B.; Gareau, Y.; Ruel, R. Reduction of olefins on solid support using diimide. *Tetrahedron Lett.* **1998**, *39*, 6785−6786. (b) Buszek, K. R.; Brown, N. Improved method for the diimide reduction of multiple bonds on solid-supported substrates. *J. Org. Chem.* **2007**, *72*, 3125−3128.

(22) Varamini, P.; Goh, W. H.; Mansfeld, F. M.; Blanchfield, J. T.; Wyse, D. B.; Smith, M. T.; Toth, I. Peripherally acting novel lipo-endomorphin-1 peptides in neuropathic pain without producing constipation. *Bioorg. Med. Chem.* **2013**, *21*, 1898−1904.