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Synthesis of Small Tripeptide Molecules through a Catalysis Sequence Comprising Metathesis and Aminohydroxylation

Jan Streuff,[a, b] Martin Nieger,[c] and Kilian Muñiz*[a, b]

Abstract: Tripeptidic structures were synthesized by using a combination of two independent consecutive catalytic procedures. Cross-metathesis of *N*-acroyl amino acid esters yields fumaric amide compounds with exclusive *E* double-bond geometry. This represents an unprecedented example of complete double-bond selectivity in this kind of reaction. A subsequent asymmetric aminohydroxylation of the chiral fumaric amides was carried out without the need of any further ligand and gave high yields and no side products. This reaction transforms the central fumaric amide unit into a hydroxy aspartic acid moiety and relies on the inherent stereochemistry of the starting fumaric diamides. An additional feature of our sequence is the ease of generating stereochemical diversification within the aminohydroxylation reaction. As a consequence, rapid conformational and configurational diversification can be achieved from the overall two-step catalytic sequence. The versatility of this approach is demonstrated by starting from two different *N*-acroyl amino esters, which led to the synthesis of eight structurally and stereochemically different tripeptides that could all be identified individually. As such, the present two-step catalytic approach should serve to efficiently synthesize large families of tripeptidic molecular probes.

Keywords: amino acids · aminohydroxylation · homogeneous catalysis · metathesis · organocatalysis · peptides

Introduction

Recent impressive advances in the area of chemical biology rely on small organic molecules employed as probes for the systematic exploration of biological functions.[1,2] To efficiently address a given biological question, there is a demand for the synthesis of configurationally and conformationally defined molecular entities. To this end, Schreiber and co-workers have introduced the concept of diversity-oriented synthesis.[3] The basic principle in this approach consists of accessing complex and structurally diverse compounds through defined organic synthesis procedures.

From this point of view, a sequence of different catalytic transformations would definitely be a strategic asset toward the realization of this goal. On the other hand, to target biomolecules or related chiral substances requires matching of the stereochemistry between the target molecule itself and the probe. Hence, there is a demand for stereochemical diversity within a given set of conformationally designed entities. Herein, we present a two-step sequence of catalytic transformations that readily generates stereochemically diverse tripeptides through a sequence of two defined catalytic processes.

Such an approach is of importance since the synthesis of natural peptides and novel peptide derivatives as well as the study of their structural properties and their biological and pharmaceutical evaluation[4] is of paramount importance for modern society. In particular, evaluation of small peptidic structures has recently emerged as a powerful tool for elucidation of biological response.[5,6] Generally, these compounds are obtained from iterative coupling of individual amino acid entities upon the application of activating agents and protecting groups.[4c,d] For the synthesis of peptides incorporating non-natural amino acids, the same sequential

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approach starting from the particular monomer is usually employed.[7]

To construct tripeptide derivatives, a sequence of two catalytic processes[8] was envisioned consisting first of a coupling of two amino acid units upon introduction of a prochiral spacer. Asymmetric transformation of this spacer should then create a new amino acid entity and thereby generate a tripeptide molecule (Figure 1, left). This approach will be particularly valuable in generating structures that contain non-natural amino acids and that are not readily accessible through conventional coupling. As another important feature, the final catalytic transformation may generate more than a single stereoisomer leading to several enantiopure tripeptides due to the initial amino acid residues (Figure 1, right). Such a modular approach should therefore meet the criteria for stereochemical diversity[5] if we intentionally choose substrates or catalysts that bring about the formation of more than a single stereoisomeric product. As such, complete configurational diversity should be feasible for those processes that produce all stereochemically possible amino acid entities at once. Thus, a potential application in biological screening processes will be able to evaluate all absolute configurations.

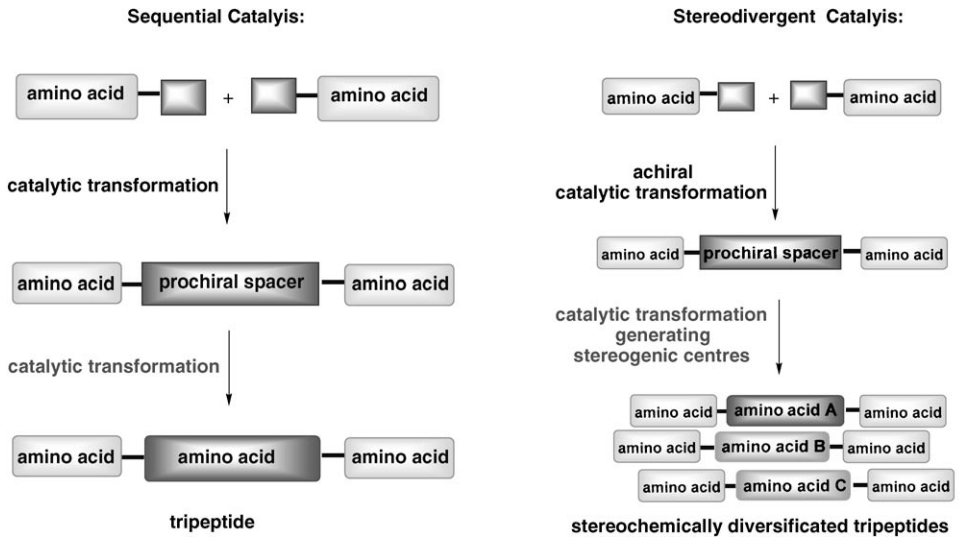


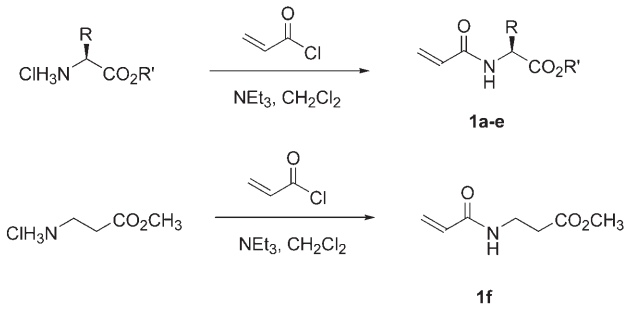
Figure 1. Concept for tripeptide synthesis employing catalytic transformations: fundamental two-step sequence (left), diversity-generating processes (right).

Results and Discussion

To achieve our goal olefin metathesis was chosen for the first transformation. Over the years, olefin metathesis has developed into one of the most broadly applicable tools in synthesis. For their outstanding contributions to the initiation and the development of olefin metathesis, Chauvin, Grubbs, and Schrock were awarded the Nobel Prize in Chemistry in 2005.[9]

Recent impressive advances in the area of olefin metathesis have led to the development of ruthenium- and molybdenum-based catalysts that enable the construction of a broad variety of alkenes within cross-metathesis.[10] To realize the concept outlined in Figure 1, fumaroyl was chosen as spacer. Fumaroyl should be accessible through catalytic homo-cross-metathesis of acrylamides incorporating amino acids. For this purpose a number of amino acids were condensed with acryl chloride under standard conditions (CH_2Cl_2, NEt_3, room temperature), which furnished the respective *N*-acroyl amino acid esters **1a–f** of alanine, phenylalanine, valine, leucine, *tert*-leucine, and β-alanine (Scheme 1).

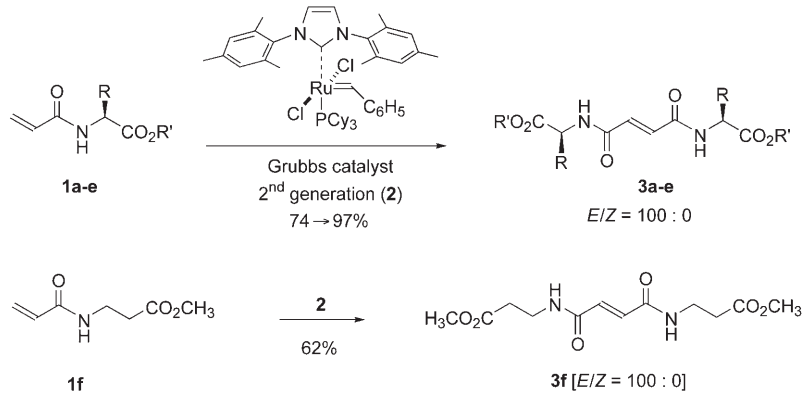
Acryl amides have not been among the more popular substrates for metathesis processes. In fact, they were regarded as rather problematic alkenes, and to date there is only a single report on their general use in cross-metathesis with other alkenes.[11] First experiments revealed that the desired homo-cross-coupling of the acryloyl alanine ester did not go to completion with the standard



Scheme 1. Synthesis of *N*-acroyl amino esters.

Grubbs catalyst [$(PCy_3)_2RuCl_2$=CHPh]. However, the corresponding second-generation catalyst **2** containing an *N*-heterocyclic carbene substituent proved to be highly efficient and, at 2.5 mol% loading, induced the formation of the desired fumaric amides (Scheme 2, Table 1).

In general, the homo-cross-metathesis reaction with catalyst **2** proceeded smoothly in refluxing dichloromethane and yielded the respective fumaroyl-linked amino acid products **3a–f** in good to excellent yields (Scheme 2). In particular, the respective products from alanine and phenylalanine gave quantitative conversion under these conditions and 94–97% isolated yield (Table 1, entries 1,2). Other examples led to incomplete yields after a reaction time of 10 h with



Scheme 2. Synthesis of amino-acid-incorporated fumaric amides through catalytic homo-cross-coupling.

Table 1. Cross-metathesis of *N*-acroyl amino esters.

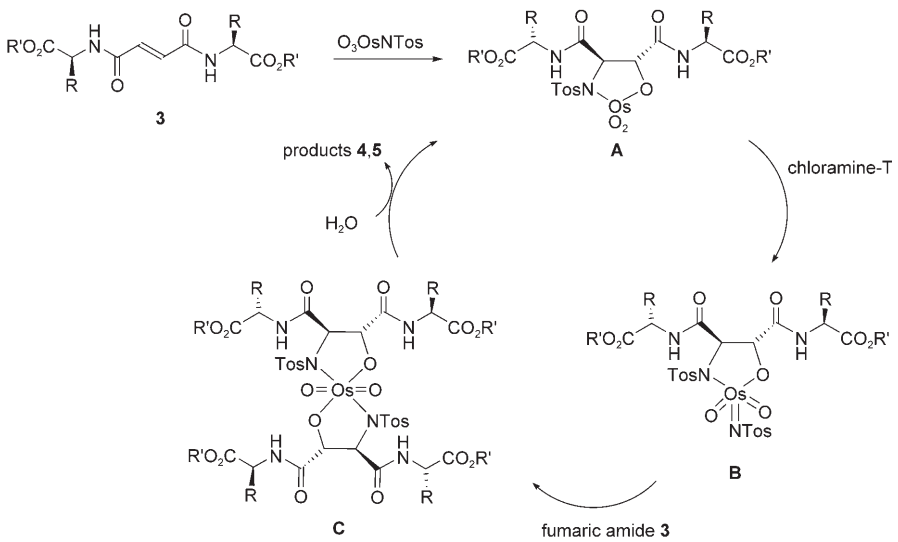
Entry	Substrate/amino acid	R	R′	Product	Yield [%]
1[a,b]	**1a**/alanine	CH_3	CH_3	**3a**	94
2[a,b]	**1b**/phenylalanine	$CH_2(C_6H_5)$	CH_2CH_3	**3b**	97
3[a]	**1c**/leucine	$CH(CH_3)_2$	CH_3	**3c**	79 (92)[c]
4[a]	**1d**/valine	$CH_2CH(CH_3)_2$	CH_3	**3d**	80 (89)[c]
5[a]	**1e**/*tert*-leucine	$C(CH_3)_3$	CH_3	**3e**	74 (84)[c]

[a] Reactions were carried out on a 1 mmol scale with 2.5 mol% of catalyst **2** in dichloromethane (2 M solution), at 40 °C and for 10 h. [b] Reaction time of 4 h. [c] Estimated conversion according to the ^{1}H NMR spectrum of the crude reaction mixture.

the remaining starting material in the range of 8–15% as estimated from the ^{1}H NMR spectra of the crude material (Table 1, entries 4,5 and 35% in the formation of product **3f** from β-alanine incorporation). In these cases, analytically pure products **3d–f** were obtained directly through crystallization from the reaction mixture or after column chromatography.[12] Importantly, all products were obtained as pure fumaric amides, that is, with complete *E* selectivity with regard to the newly established C=C double bond. Given the usual reversibility of transition-metal-catalyzed metathesis, this rarely observed complete selectivity may be attributed to the high insolubility of the product in the reaction solvent. Alternatively, a decisive influence of the amide group on the final *E*/*Z* selectivity through additional interaction with the metal center cannot be ruled out at the present stage.

The catalytic metathesis step with its well-defined product formation poses the interesting question on subsequent use of the products as starting materials for oxidative alkene conversion.[13] Transformation of products **3a–f** into peptidic structures requires nitrogen incorporation. Recent advances in the aminohydroxylation[14] of unsaturated esters have led to the synthesis of various serine and isoserine derivatives, of which the side chain of Paclitaxel represents the most prominent example.[15] Still, this reaction generates amino acid monomers that require elaboration within the usual coupling processes. On the other hand, unsaturated amides represent a unique class of starting compounds for Sharpless aminohydroxylation within the so-called second catalytic cycle. This reaction forms serine and isoserine amides in racemic form only and due to the specific oxidation conditions of second cycle catalysis cannot be carried out enantioselectively.[16,17]

However, the realization of an aminohydroxylation reaction course toward chiral non-racemic molecules should in principle be feasible by the use of an enantiopure α,β-unsaturated starting material as is the case for **3a–e**. A catalytic cycle will begin with an aminohydroxylation to give an osma(VI)azaglycolate **A**, which subsequently functions as a catalyst (Scheme 3). Reoxidation to compound **B** with a central osmium(VIII) atom occurs with the nitrenoid chloramine-T. Then, subsequent aminohydroxylation of another fumaric amide occurs resulting in the formation of a bisazaglycolate

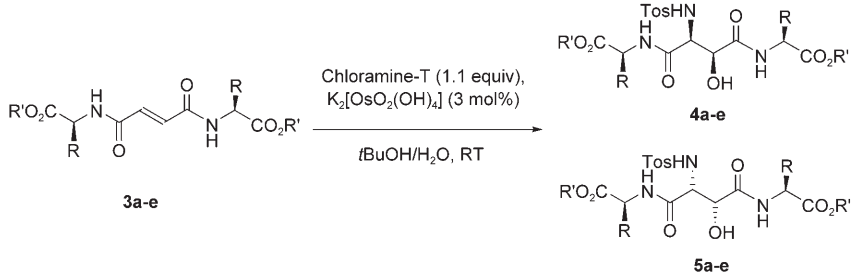


Scheme 3. Catalytic cycle for expected oxidative transformation of fumaric amides **3** into tripeptides **4**,**5**.

C. One tripeptidic product is released by hydrolysis and azaglycolate **A** is regenerated.

Any stereoselection in conventional second-cycle catalysis relies solely on the remote chiral information of glycolate

and azaglycolate ligands, respectively. In view of the generally observed low induction in the step to produce **C** from **B**, the formation of diastereomeric mixtures at stage **C** arises. We previously discussed the impossibility for high stereoselectivity in self-replication processes of related second-cycle catalysis and therefore expected the formation of both stereoisomers for the present aminohydroxylation reaction of **3a**–**e**.[18,19] Such a result is well-suited for the present purpose of a stereodiversified peptide synthesis. The synthesis has been achieved for enantiopure fumaric amides **3a**–**e** incorporating amino acid residues, which upon aminohydroxylation directly and exclusively yield two diastereomeric tripeptides with hydroxy aspartic acid incorporated as bridging entity (Scheme 4).



Scheme 4. Asymmetric aminohydroxylation of chiral fumaric amides.

In all cases, quantitative conversion was achieved and no products other than the expected β-hydroxy aspartic acid derivatives were observed. Depending on the original amino acid residues, different diastereomeric ratios (d.r.) were observed that ranged from 55:45–85:15 (Table 2). As expected

Table 2. Aminohydroxylation of amino acid based fumaric amides.

Entry	Substrate	Products	Conversion [%][a]	d.r.[b]
1	**3a**	**4a, 5a**	>99	67:33
2	**3b**	**4b, 5b**	>99	62:38
3	**3c**	**4c, 5c**	>99	85:15
4	**3d**	**4d, 5d**	>99	55:45
5	**3e**	**4e, 5e**	>99	58:42

[a] Determined by ^{1}H NMR spectroscopy and TLC. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

from the literature,[16] the usually employed chiral *cinchona* alkaloid ligands[14] did not influence the diastereomeric ratios. The incomplete stereoselectivity was expected for the present project, since product diversification demands the formation of diastereomeric mixtures.[20] For the purpose of full characterization, all product mixtures **4**/**5** could be readily separated, either by conventional silica-gel column chromatography or by semi-preparative HPLC on a silica-gel phase.

β-Hydroxy aspartic acid with its particular functional groups represents a structural chimera classified as α-amino acid, β-amino acid, α-hydroxy, and β-hydroxy acid, respectively. To our surprise, no X-ray data on a small organic molecule incorporating the structural connection present here was available from the CCDC.[21] Therefore, the major isomer from aminohydroxylation of fumaric amide **3c** was crystallized and its absolute *S,S,S,S* configuration was unambiguously established by X-ray analysis (Figure 2).

The asymmetric unit contains four independent molecules that differ in the respective orientation of their leucine units. As a common motif there is a single intramolecular hydrogen bond present, which is located between the OH group of the central β-hydroxyl aspartic acid moiety and the ester group of a valine terminus producing a nine-membered helical arrangement. While for three of the molecules this connects to the carbonyl group (Figure 2, top), the remaining structure shows a hydrogen bridge to the methoxy group (Figure 2, bottom). This intramolecular hydrogen bridge between the OH group of the newly generated amino acid and the ester of one valine unit determines the overall structure of the molecule. All remaining

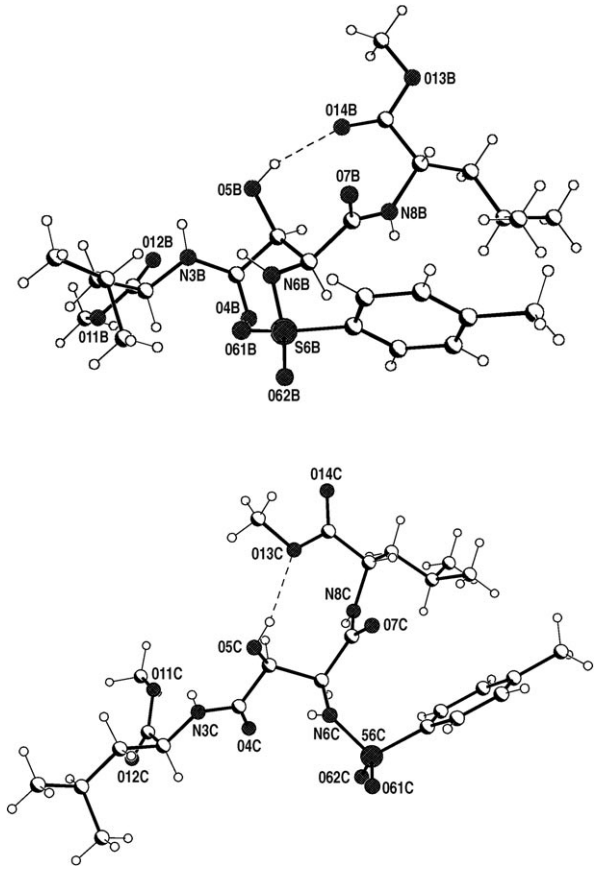


Figure 2. Solid-state structure of (*S,S,S,S*)-**4c**. Two of four independent molecules from the asymmetric unit.

hydrogen bonds are intermolecular bridging bonds resulting in a typical β-sheet arrangement. Figure 3 displays the central entity of the four independent molecules. Two molecules

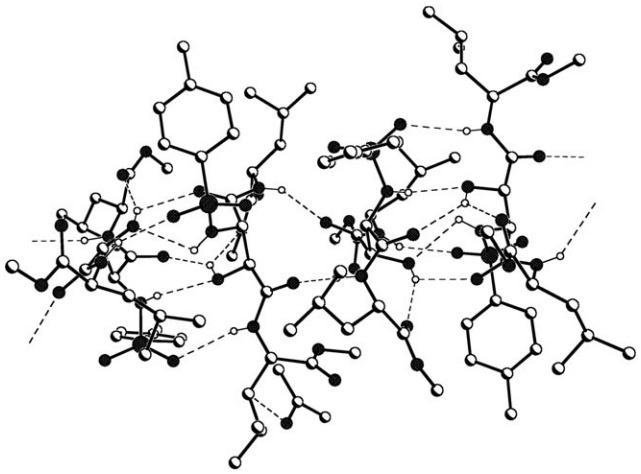


Figure 3. Intermolecular-hydrogen-bonding pattern for [(*S,S,S,S*)-**4c**]$_4$·acetone.

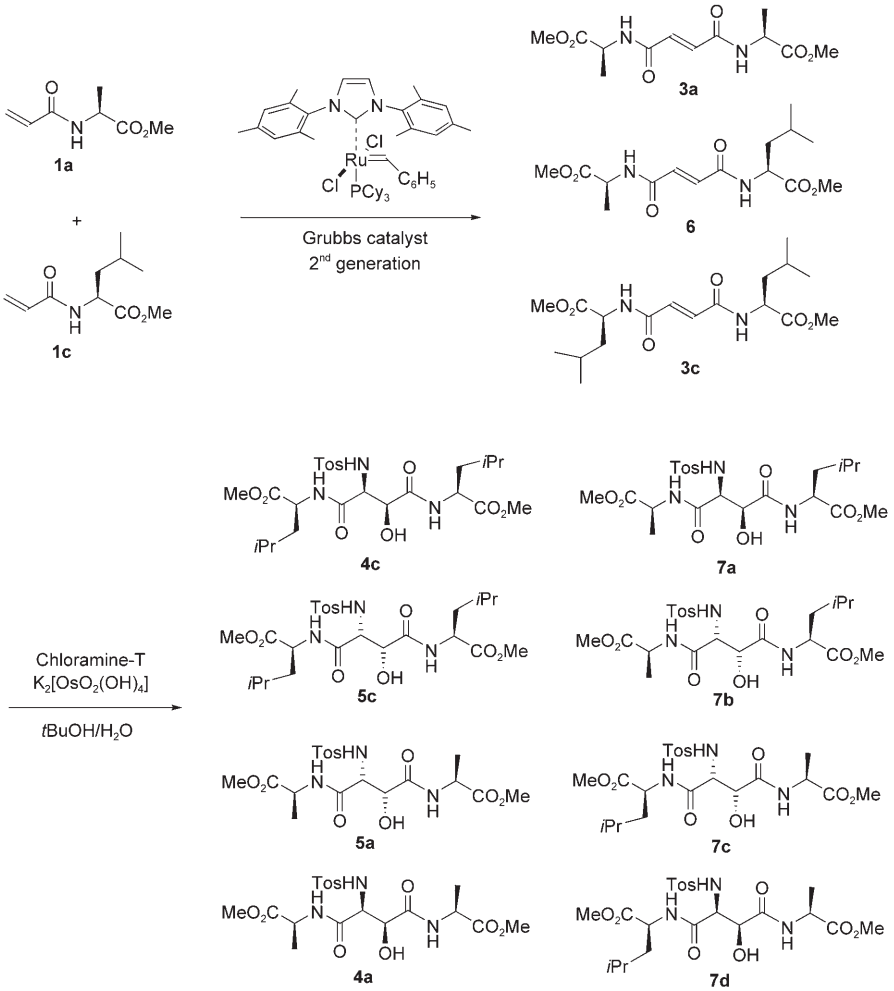
are connected to form an antiparallel sheet structure through six intermolecular hydrogen bonds. These involve five N−H and one O−H moieties. A common observation is that the involvement of the latter renders the intermolecular hydrogen bonds to be of bifocal character.[22] The resulting two sheet structures are again orientated in an antiparallel fashion towards each other through two additional NH−OC bonds.

These examples of generating enantiomerically pure compounds **4a–d** and **5a–d** prove that structural diversification of small molecules based on tripeptides is quite possible within two consecutive catalytic transformations. In addition, the asymmetric aminohydroxylation relies on the inherent stereochemical information provided by the amino acid residues from the fumaric amide substrates. Thus, no further source of chirality is required, which renders the present conversion highly economical.[23] In principle, an even higher diversification should be possible from the reaction of fumaric amides with differentiation with regard to the absolute amino acid configuration or the amino acid residues themselves.

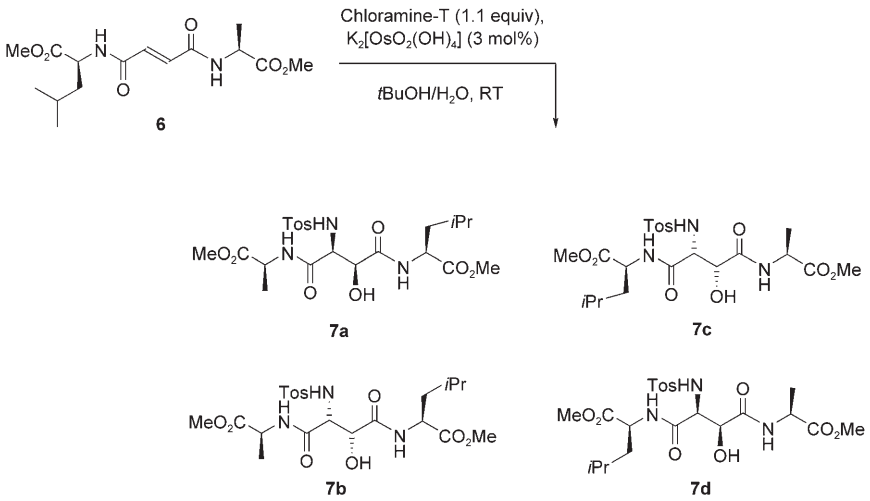
To demonstrate the high potential of this approach, we conducted a cross-metathesis of *N*-acryl alanine and *N*-acryl leucine, which furnished all three different fumaric amides in the expected statistical ratio of 1:1:2. Subsequent aminohydroxylation of the three unseparated compounds then led to formation of a mixture of all eight possible different tripeptides within a single aminohydroxylation step, which could be identified unambiguously by HLPC analysis (Scheme 5).[24]

Again, the individual components could be characterized by starting from the isolation of the mixed fumaric amide **6**. Subsequent aminohydroxylation of the asymmetric fumaric amide **6** led to complete conversion with no detection of side products. As expected, all four possible isomers **7a–d** were obtained in a 38:12:38:12 ratio and could be conveniently separated (Scheme 6).

After having obtained the respective tripeptide from the oxidations of **3a** and **3c** (Table 2, entries 1 and 3), all eight



Scheme 5. Generation of eight different tripeptides from sequential catalytic transformation of two *N*-acroyl amino esters.



Scheme 6. Synthesis of tripeptides from mixed fumaric amide **6**.

tripeptides from aminohydroxylation of the unseparated reaction mixture from metathesis could thus be isolated and characterized.

Conclusions

We have described a two-step catalytic process leading to the preparation of chiral, optically active tripeptides within two consecutive catalytic reactions and in high overall yields. The formation of the additional stereogenic centers relies solely on the inherent stereochemistry of the incorporated amino acids and represents the proof of principle for this new conceptual approach in peptide synthesis. Moreover, it can be used as a powerful synthesis tool to promote stereochemical diversity in the generation of novel peptides, both as individual compounds in an analytically pure form and as diversified mixtures for potential biological screening.

Experimental Section

^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX 300 MHz or a Bruker DPX 400 MHz spectrometer. The ^{1}H and ^{13}C NMR chemical shifts were referenced to the solvent signals (^{1}H NMR: $CDCl_3$ = 7.26, [D_6]DMSO = 2.49, [D_4]methanol = 3.30 ppm. ^{13}C NMR: $CDCl_3$ = 77.00, [D_6]DMSO = 39.50, [D_4]methanol = 49.00 ppm). The mass spectra and the high-resolution mass spectra were measured on a Kratos MS 50 mass spectrometer. The polarization angle was obtained by using a Perkin–Elmer PE-241 polarimeter. All measurements were obtained at room temperature by using a Na-lamp with a wavelength at 589 nm. The sample length was d = 10 cm and the concentration is given in g mL^{-1}. HPLC determinations and separations were carried out on a Knauer Wellchrome instrument (injection valve A0258, pump K-100, solvent organiser K-1500, UV-detector K-2600) by using Eurosphere columns as standard columns for semi-preparative separations.

General procedures

Representative procedure A for cross-metathesis: A flame-dried Schlenk flask was equipped with a magnetic stirrer bar, a reflux condenser, and was set under argon atmosphere. The second-generation Grubbs catalyst (0.05 equiv) was dissolved in absolute dichloromethane and the *N*-substituted acrylic amide was added to the dark violet solution (2.00 equiv, [amide] ≈ 0.5 mmol mL^{-1}). The mixture was refluxed for about 6 h and the metathesis reaction initiated after a couple of minutes. When the reaction was finished (TLC control), the solvent was removed under reduced pressure and the conversion was estimated by NMR measurements performed on the crude material. The crude precipitate was purified by recrystallization from dichloromethane/hexanes unless otherwise stated. The products were usually obtained as a white solid.

Representative procedure B for aminohydroxylation: The fumaric acid diamide (1.00 equiv) was suspended in a mixture of *t*BuOH/H_2O (1:1) and Chloramine-T hydrate (1.10 equiv) was added. After a few minutes of stirring, $K_2[OsO_2(OH)_4]$ (0.03 equiv) was added and stirring was continued until the reaction was complete (controlled by TLC). A small amount of saturated $Na_2S_2O_3$ solution was added to quench the reaction and stirring was continued for 20 min. The mixture was extracted several times with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and an NMR spectrum of the crude yellow-white product was taken to calculate the diastereomeric excess. The stereoisomers were separated by flash chromatography and/or semi-preparative HPLC chromatography as specified in the procedures.

Representative procedure C for the synthesis of *N*-monosubstituted acryl amides: A flame-dried Schlenk flask was equipped with a magnetic stirrer bar and set under argon atmosphere, then freshly distilled dichloromethane (100 mL) and triethylamine (6.23 mL, 45 mmol, 4.5 equiv) were added. The primary amine (1.0 equiv, 10 mmol) was dissolved in this mixture and the solution was cooled down to −10 °C. Then acroyl chloride (1.22 mL, 15 mmol, 1.5 equiv) was added dropwise. The solution was allowed to warm to room temperature and was stirred for 4 h. The color of the solution changed from a light green-yellow to orange-red. The reaction was quenched by the addition of HCl solution and additional washing with HCl (3.5 %), and the separated organic layer was washed several times with saturated Na_2CO_3 solution. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography when necessary.

(*S*)-*N*-1-Methoxycarbonylethylacrylamide (*N*-acryloyl-L-alanine methyl ester) (1a):[25]

Compound **1a** was synthesized according to general procedure C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, J = 7.1 Hz, 3H), 3.75 (s, 3H), 4.68 (m, 1H), 5.66 (ddd, J_1 = 10.4 Hz, J_2 = 1.5 Hz, J_3 = 0.8 Hz, 1H), 6.12 (dd, J_1 = 16.9 Hz, J_2 = 10.4 Hz, 1H), 6.29 ppm (dd, J_1 = 16.9 Hz, J_2 = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.49, 48.03, 52.48, 127.00, 130.39, 164.82, 173.51 ppm.

(*S*)-*N*-1-Ethoxycarbonyl-2-phenylethylacrylamide (*N*-acryloyl-L-phenylalanine ethyl ester) (1b):[26] Compound **1b** was synthesized according to general procedure C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3H), 3.10 (dd, J_1 = 5.6 Hz, J_2 = 2.3 Hz, 2H), 4.11 (dq, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 2H), 4.87 (td, J_1 = 5.6 Hz, J_2 = 7.8 Hz, 1H), 5.59 (dd, J_1 = 10.4 Hz, J_2 = 1.3 Hz, 1H), 6.02 (dd, J_1 = 16.9 Hz, J_2 = 10.4 Hz, 1H), 6.21 (dd, J_1 = 16.9 Hz, J_2 = 1.3 Hz, 1H), 7.03 (m, 2H), 7.19 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.09, 37.91, 53.18, 61.58, 127.06, 127.09, 128.49, 129.35, 130.39, 135.81, 164.84, 171.47 ppm.

(*S*)-*N*-1-Methoxycarbonyl-2-isopropylethylacrylamide (*N*-acryloyl-L-leucine methyl ester) (1c): Compound **1c** was synthesized according to general procedure C.

$[\alpha]_D^{25} = -34.9$ ($c = 1.00$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (dd, $J_1 = 6.4$ Hz, $J_2 = 4.2$ Hz, 6H), 1.50–1.71 (m, 3H), 3.73 (s, 3H), 4.72 (td, $J_1 = 8.5$ Hz, $J_2 = 5.1$ Hz, 1H), 5.65 (dd, $J_1 = 10.2$ Hz, $J_2 = 1.7$ Hz, 1H), 6.12 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.2$ Hz, 1H), 6.29 ppm (dd, $J_1 = 17.0$ Hz, $J_2 = 1.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.95$, 22.72, 24.85, 41.77, 50.69, 52.27, 127.04, 130.34, 165.12, 173.58 ppm; IR (KBr): $\tilde{\nu} = 3272$, 3067, 2958, 2914, 2873, 1749, 1659, 1630, 1547, 1255, 1209, 1153, 985 cm^{-1}; MS (EI): *m*/*z* (%): 199.2 $[M]^+$, 184.1 (2), 168.1 (2), 156.1 (3), 143.1 (16), 140.1 (100), 124.1 (4), 111.1 (10), 98.1 (4), 86.1 (75), 84.1 (6), 72.1 (4), 59.1 (2), 55.1 (62); HRMS: calcd: 199.1208; found: 199.1212.

(*S*)-*N*-1-Methoxycarbonyl-2,2-dimethylethylacrylamide (*N*-acryloyl-L-valine methyl ester) (1d):[25b] Compound **1d** was synthesized according to general procedure C.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (dd, $J_1 = 8.1$ Hz, $J_2 = 6.8$ Hz, 6H), 2.15 (m, 1H), 3.71 (s, 3H), 4.62 (dd, $J_1 = 8.9$ Hz, $J_2 = 5.1$ Hz, 1H), 5.63 (dd, $J_1 = 10.0$ Hz, $J_2 = 1.9$ Hz, 1H), 6.15 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.0$ Hz, 1H), 6.30 ppm (dd, $J_1 = 17.0$ Hz, $J_2 = 1.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.81$, 18.82, 31.33, 52.05, 57.02, 126.93, 130.42, 165.27, 172.48 ppm.

(*S*)-*N*-1-Methoxycarbonyl-1-*tert*-butylmethyl-acrylamide (*N*-acryloyl-L-*tert*-leucine methyl ester) (1e): Compound **1e** was synthesized according to general procedure C. The crude product was purified by flash chromatography (EtOAc/hexanes 1:1, 80% isolated yield). $[\alpha]_D^{23} = -37.5$ ($c = 0.49$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (s, 9H), 3.73 (s, 3H), 4.57 (d, $J = 9.4$ Hz, 1H), 5.68 (dd, $J_1 = 10.1$ Hz, $J_2 = 1.5$ Hz, 1H), 6.07 (br s, 1H; N*H*), 6.15 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.1$ Hz, 1H), 6.30 ppm (dd, $J_1 = 17.0$ Hz, $J_2 = 1.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.54$, 35.00, 51.83, 59.86, 127.12, 130.52, 165.09, 172.12 ppm; IR (KBr): $\tilde{\nu} = 3301$, 3062, 3034, 2968, 2910, 2875, 1743, 1654, 1619, 1544, 1413, 1261, 1238, 1219, 1162, 1115, 991 cm^{-1}; MS (EI): *m*/*z* (%): 199.1 $[M]^+$, 184.1 (2), 168.1 (2), 156.1 (0), 152.0 (6), 143.0 (100), 140.1 (20), 124.1 (4), 111.0 (84), 97.0 (2), 86.1 (30), 83.0 (16), 73.1 (2), 70.1 (4), 57.1 (18), 55.0 (36); HRMS: *m*/*z* calcd: 143.0582 $[M^+ - C(CH_3)_3]$; found: 143.0583.

***N*-2-Methoxycarbonylethylacrylamide (*N*-acryloyl-*b*-alanine methyl ester) (1f)**: Compound **1f** was synthesized according to general procedure C.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.53$ (t, $J = 6.0$ Hz, 2H), 3.53 (psq, $J = 6.0$ Hz, 2H), 3.63 (s, 3H), 5.55 (dd, $J_1 = 10.0$ Hz, $J_2 = 1.9$ Hz, 1H), 6.06 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.0$ Hz, 1H), 6.20 (dd, $J_1 = 17.0$ Hz, $J_2 = 1.9$ Hz, 1H), 6.56 ppm (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.61$, 34.83, 51.61, 126.18, 130.73, 165.50, 172.77 ppm; IR (KBr): $\tilde{\nu} = 3284$, 3074, 2954, 1738, 1660, 1628, 1549, 1439, 1244, 1200, 1178, 1084, 987 cm^{-1}; MS (EI): *m*/*z* (%): 157.1 $[M]^+$, 126.1 (16), 102.1 (56), 98.1 (16), 88.1 (4), 86.0 (8), 84.1 (35), 72.1 (5), 70.1 (10), 59.1 (4), 55.1 (100); HRMS: *m*/*z* calcd: 157.0739; found: 157.0740.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylethyl]fumaric diamide (3a)**: Compound **3a** was synthesized according to general procedure A with 0.05 equivalents of catalyst. The crude product was purified by recrystallization from CH_2Cl_2/hexanes (94% yield).

$[\alpha]_D^{23} = -44$ ($c = 0.1$, DMSO); ^{1}H NMR (300 MHz, [D$_6$]DMSO/[D$_4$]methanol): $\delta = 1.30$ (d, $J = 7.2$ Hz, 6H) 3.62 (s, 6H) 4.35 (qd, $J_1 = 7.2$ Hz, $J_2 = 7.2$ Hz, 2H), 6.87 (s, 2H) 8.81 ppm (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO/[D$_4$]methanol): $\delta = 16.80$, 47.75, 51.87, 132.49, 163.36, 172.65 ppm; IR (KBr): $\tilde{\nu} = 3304$, 3080, 3066, 3049, 2999, 2954, 2935, 2885, 2852, 1734, 1630, 1554, 1539, 1456, 1358, 1338, 1279, 1227, 1198, 1119, 1057, 991, 688, 667 cm^{-1}; MS (EI): *m*/*z* (%): 286.1 $[M]^+$, 255.1 (4), 227.1 (100), 184.0 (30), 125.0 (8), 124.0 (60), 96.0 (3), 82.0 (4), 70.0 (4), 59.0 (3); HRMS: *m*/*z* calcd for $C_{12}H_{18}N_2O_6$: 286.1165; found: 286.1169.

***N*,*N*′-Bis[(*S*)-1-(ethoxycarbonyl)-2-phenylethyl]fumaric diamide (3b)**: Compound **3b** was synthesized according to general procedure A with 0.05 equivalents of catalyst. The crude product was purified by recrystallization from CH_2Cl_2/hexanes (97% yield).

$[\alpha]_D^{23} = -29$ ($c = 0.14$, DMSO); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.10$ (t, $J = 7.0$ Hz, 6H), 2.90 (dd, $J_1 = 14,0$ Hz, $J_2 = 9.1$ Hz, 2H), 3.05 (dd, $J_1 = 14.0$ Hz, $J_2 = 5.8$ Hz, 2H), 3.14 (quin, $J = 1.6$ Hz, 2H), 4.03 (q, $J = 7.2$ Hz, 4H), 4.55 (dd, $J_1 = 9.1$ Hz, $J_2 = 5.8$ Hz, 2H), 6.80 (s, 2H) 7.14–7.24 ppm (m, 10H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 14.10$, 54.60, 61.35, 127.16, 128.80, 129.57, 133.14, 137.60, 164.53, 171.74 ppm; IR (KBr): $\tilde{\nu} = 3311$, 3064, 3030, 2978, 1736, 1630, 1539, 1377, 1354, 1201, 1119, 1024, 698 cm^{-1}; MS (EI): *m*/*z* (%): 466.2 $[M]^+$, 421.1 (35), 393.1 (65), 375.1 (15), 350.2 (20), 304.2 (1), 291.1 (3), 290.1 (10), 274.1 (25), 246.1 (2), 228.0 (2), 217.1 (4), 200.0 (30), 182.0 (5), 177.1 (15), 176.1 (100), 148.0 (8), 131.0 (12), 120.1 (30), 103.0 (8), 91.0 (15), 82.0 (6); HRMS: *m*/*z* calcd for $C_{26}H_{30}N_2O_6$: 466.2104; found: 466.2111.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonyl-1-isobutylmethyl]fumaric diamide (3c)**: Compound **3c** was synthesized according to general procedure A with 0.025 equivalents of catalyst. The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc 1:1, 79% yield).

$[\alpha]_D^{23} = -62$ ($c = 0.23$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (dd, $J_1 = 6.2$ Hz, $J_2 = 1.9$ Hz, 12H), 1.50–1.74 (m, 6H), 3.75 (s, 6H), 4.73 (dt, $J_1 = 8.7$, $J_2 = 4.7$ Hz, 2H), 6.61 (d, $J = 8.7$ Hz, 2H), 6.90 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.87$, 22.80, 24.92, 41.48, 51.04, 52.46, 133.11, 163.77, 173.49 ppm; IR (KBr): $\tilde{\nu} = 3548$, 3467, 3417, 3319, 3062, 2960, 2889, 1753, 1738, 1635, 1535, 1439, 1280, 1255, 1185, 997 cm^{-1}; MS (EI): *m*/*z* (%): 370.2 $[M]^+$, 355.2 (5), 339.2 (5), 311.2 (100), 226.1 (40), 183.1 (5), 166.1 (25), 146.1 (8), 124.0 (10), 110.0 (10), 98.0 (8), 86.1 (56), 69.1 (10); HRMS: *m*/*z* calcd for $C_{18}H_{30}N_2O_6$: 370.2104; found: 370.2111.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonyl-1-iso-propyl-methyl]fumaric diamide (3d)**: Compound **3d** was synthesized according to general procedure A with 0.05 equivalents of catalyst. The crude product was dissolved in CH_2Cl_2 and hexanes were added to cause precipitation. The white solid was filtered off and purified by flash chromatography (ethyl acetate) to separate it from the remaining ruthenium salts (80% yield).

$[\alpha]_D^{23} = -50.7$ ($c = 0.44$, methanol); ^{1}H NMR (300 MHz, [D$_4$]methanol): $\delta = 0.96$ (dd, $J_1 = 6.8$ Hz, $J_2 = 1.3$ Hz, 12H), 2.17 (heptet, $J = 6.8$ Hz, 2H), 3.72 (s, 6H), 4.41 (d, $J_1 = 6.0$ Hz, 2H), 7.04 ppm (s, 2H); ^{13}C NMR (75 MHz, [D$_4$]methanol): $\delta = 18.52$, 19.43, 31.85, 52.53, 59.66, 133.97, 166.80, 173.21 ppm; IR (KBr): $\tilde{\nu} = 3298$, 3070, 2968, 1741, 1639, 1547, 1437, 1356, 261, 1207, 1196, 991 cm^{-1}; MS (EI): *m*/*z* (%): 342.2 $[M]^+$, 283.1 (100), 229.1 (12), 212.1 (38), 169.1 (17), 152.0 (40), 132.1 (6), 98.0 (10), 82.0 (10), 72.1 (50); HRMS: *m*/*z* calcd for $C_{16}H_{26}N_2O_6$: 342.1791; found: 342.1794.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonyl-2,2-dimethylpropyl]fumaric diamide (3e)**: Compound **3e** was synthesized according to general procedure A with 0.025 equivalents of catalyst. The crude product was purified by recrystallization from CH_2Cl_2/hexanes (73.5% isolated yield).

$[\alpha]_D^{23} = -34$ ($c = 0.65$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (s, 18H), 3.74 (s, 6H), 4.59 (d, $J = 9.4$ Hz, 2H), 6.36 (d, $J = 9.4$ Hz, 2H), 6.95 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.54$, 35.15, 51.96, 60.25, 133.30, 163.61, 171.60 ppm; IR (KBr): $\tilde{\nu} = 3550$, 3475, 3413, 2966, 2916, 2875, 1741, 1639, 1533, 1369, 1230, 1188, 1169 cm^{-1}; MS (EI): *m*/*z* (%): 355.1 $[M^+ - CH_3]$, 339.1 (4), 314.1 (10), 311.1 (12), 227.0 (100), 195.0 (4), 167.0 (8), 146.0 (5), 98.0 (5), 86.0 (8), 69.0 (4), 57.1 (4); HRMS: *m*/*z* calcd for $C_{17}H_{27}N_2O_6$: 355.1869; found: 355.1875.

***N*,*N*′-Bis(2-methoxycarbonylethyl)fumaric diamide (3f)**: Compound **3f** was synthesized according to general procedure A with 0.05 equivalents of catalyst. The crude product was purified by recrystallization from CH_2Cl_2/hexanes (62% yield).

^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.56$ (t, $J_1 = 6.8$ Hz, 6H), 3.36 (dt, $J_1 = 6.8$ Hz, $J_2 = 5.7$ Hz, 4H), 3.59 (s, 6H), 6.77 (s, 2H), 8.47 ppm (t, $J = 5.7$ Hz, 2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 33.34$, 34.90, 51.32, 132.40, 163.70, 171.52 ppm; IR (KBr): $\tilde{\nu} = 3259$, 3080, 2958, 1726, 1626, 1562, 1441, 1346, 1194, 1174, 1088, 976, 887 cm^{-1}; MS (EI): *m*/*z* (%): 286.1 $[M]^+$, 257.1 (2), 255.1 (56), 227.1 (10), 213.0 (10), 195.0 (2), 185.0 (100), 171.0 (2), 157.0 (3), 156.0 (8), 152.0 (46), 127.0 (4), 125.0 (10), 110.0 (62), 102.0 (54), 98.0 (10), 81.9 (14), 70.0 (8), 55.0 (15); HRMS: *m*/*z* calcd for $C_{12}H_{18}N_2O_6$: 286.1165; found: 286.1164.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylethyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)-succinic diamide (5a) and *N*,*N*′-bis[(*S*)-1-methoxycarbonylethyl]-**

(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4a): Compound **4a** was synthesized according to general procedure B. Stereoisomer 1 was isolated by recrystallization from methanol. The NMR data for stereoisomer 2 were deduced from the NMR data of the remaining mixture that was enriched in stereoisomer 2.

Stereoisomer 1: $[\alpha]_D^{23} = -34$ ($c = 0.14$, MeOH); ^{1}H NMR (300 MHz, [D$_4$]methanol): $\delta = 1.26$ (d, $J = 7.2$ Hz, 3H), 1.31 (d, $J = 7.4$ Hz, 3H), 2.41 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 4.19 (d, $J = 7.4$ Hz, 1H), 4.25 (d, $J = 7.2$ Hz, 1H), 4.30 (d, $J = 1.9$ Hz, 1H), 4.40 (d, $J = 1.9$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 2H), 7.69 ppm (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.65$, 17.72, 21.43, 52.83, 60.15, 73.27, 128.32, 130.58, 139.26, 144.85, 171.07, 172.81, 174.09, 174.36 ppm; IR (KBr): $\tilde{\nu} = 3419$, 3392, 3327, 2970, 2935, 2524, 2476, 1736, 1749, 1653, 1522, 1450, 1335, 1236, 1159, 1097, 816, 675, 544 cm^{-1}; MS (EI): m/z (%): 473.2 $[M]^+$, 442.1 (2), 424.1 (2), 414.1 (8), 396.1 (10), 378.1 (2), 371.1 (5), 353.1 (15), 343.1 (60), 314.1 (5), 293.0 (10), 283.1 (12), 253.1 (5), 235.1 (2), 214.1 (70), 200.0 (3), 189.1 (15), 171.0 (5), 161.1 (90), 159.1 (100), 155.0 (75), 139.0 (25), 114.0 (5), 104.0 (35), 91.0 (65), 70.0 (16), 60.1 (15); HRMS: m/z calcd for $C_{19}H_{27}N_3O_7S$: 473.146; found: 473. 1463.

Stereoisomer 2: ^{1}H NMR (300 MHz, [D$_4$]methanol): $\delta = 1.24$ (d, $J = 7.2$ Hz, 3H), 1.32 (d, $J = 7.2$ Hz, 3H), 2.39 (s, 3H), 3.70 (s, 3H), 3.76 (s, 3H), 4.17 (d, $J = 7.2$ Hz, 1H), 4.27 (d, $J = 7.2$ Hz, 1H), 4.32 (d, $J = 1.7$ Hz, 1H), 4.42 (d, $J = 2.3$ Hz, 1H), 7.28 (d, $J = 8.66$ Hz, 2H), 7.70 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, [D$_4$]methanol): $\delta = 17.60$, 18.09, 23.71, 53.02, 60.07, 73.00, 128.26, 130.56, 139.18, 144.80, 171.32, 172.47, 174.15, 174.25 ppm; HRMS: m/z calcd for $C_{19}H_{27}N_3O_7S$: 473.146; found: 473.1456.

***N*,*N*′-Bis[(*S*)-1-(ethoxycarbonyl)-2-phenylethyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)succinic diamide (5b) and *N*,*N*′-bis[(*S*)-1-(ethoxycarbonyl)-2-phenylethyl]-(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4b)**: Compounds **5b** and **4b** were synthesized according to general procedure B. Separation of the isomers was carried out by using flash chromatography (hexanes/EtOAc 5:2).

Stereoisomer 1: $[\alpha]_D^{23} = -37.5$ ($c = 0.50$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (td, $J_1 = 7.1$ Hz, $J_2 = 1.0$ Hz, 6H), 2.41 (s, 3H), 3.01 (m, 2H), 3.08 (m, 2H), 3.92 (dd, $J_1 = 5.6$ Hz, $J_2 = 3.5$ Hz, 1H), 4.09–4.15 (m, 4H), 4.49–4.54 (m, 1H), 4.67–4.73 (m, 1H), 4.80 (d, $J = 7.1$ Hz, 1H), 6.38 (d, $J = 8.1$ Hz, 1H), 7.02–7.04 (m, 2H), 7.13–7.32 (m, 10H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.69 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.98$, 14.02, 21.54, 37.63, 37.80, 53.03, 53.60, 56.86, 61.53, 61.68, 70.55, 127.08, 127.18, 127.24, 128.48, 128.69, 129.13, 129.28, 129.81, 135.35, 135.60, 136.52, 144.00, 170.31, 170.57, 170.60, 170.64 ppm; IR (KBr): $\tilde{\nu} =$ 3547, 3394, 3313, 3064, 3030, 2981, 2935, 1740, 1660, 1529, 1444, 1342, 1213, 1163, 1090, 1030, 702, 667, 555 cm^{-1}; MS (EI): m/z (%): 653.1 $[M]^+$, 580.1 (10), 562.1 (6), 461.0 (5), 433.0 (60), 403.0 (8), 387.0 (6), 359.0 (25), 341.0 (10), 279.0 (15), 257.0 (20), 251.0 (100), 249.0 (50), 220.0 (10), 214.0 (40), 194.0 (30), 176.0 (70), 154.9 (50), 138.9 (15), 120.0 (70), 102.0 (20), 91.0 (65), 60.0 (5); HRMS: m/z calcd for $C_{33}H_{39}N_3O_9S$: 653.2407; found: 653.2426.

Stereoisomer 2: $[\alpha]_D^{23} = +50.5$ ($c = 0.50$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ (q, $J = 7.1$ Hz, 6H), 2.38 (s, 3H), 2.90 (dd, $J_1 = 13.9$ Hz, $J_2 = 6.06$ Hz, 1H), 3.01–3.06 (m, 3H), 3.84 (dd, $J_1 = 8.8$ Hz, $J_2 = 4.0$ Hz, 1H), 4.08–4.16 (m, 4H), 4.66–4.71 (m, 2H), 4.83 (d, $J = 9.1$ Hz, 1H), 6.60 (d, $J = 9.1$ Hz, 1H), 7.07–7.32 (m, 15H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.71 ppm (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.01$, 21.53, 37.77, 38.03, 52.90, 53.67, 56.37, 61.56, 61.68, 70.58, 127.11, 127.20, 127.25, 128.59, 128.65, 129.31, 129.84, 130.02, 135.29, 136.61, 144.19, 170.08, 170.48, 170.64, 171.85 ppm; IR (KBr): $\tilde{\nu} = 3398$, 3331, 3277, 3064, 3030, 2981, 2933, 1740, 1662, 1527, 1456, 1340, 1203, 1165, 1092, 1030, 702, 667, 555 cm^{-1}; MS (EI): m/z (%): 653.2 $[M]^+$, 608.2 (5), 580.1 (20), 562.1 (10), 488.1 (10), 461.1 (12), 433.1 (10), 361.1 (15), 258.0 (15), 251.1 (75), 214.1 (50), 194.1 (30), 176.1 (95), 155.0 (60), 131.0 (20), 120.1 (70), 102.0 (35), 91.0 (100), 60.1 (10); HRMS: m/z calcd for $C_{33}H_{39}N_3O_9S$: 653.2407; found: 653.2416.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylisobutylmethyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)succinic diamide (5c) and *N*,*N*′-bis[(*S*)-1-methoxycarbonylisobutylmethyl]-(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4c)**: Compound **4c** was synthesized according to general procedure B. Separation of the isomers was achieved by flash chromatography (CH_2Cl_2/EtOAc 2:1).

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylisobutylmethyl]-(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4c)**: $[\alpha]_D^{23} = +7$ ($c = 0.5$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (m, 12H), 1.58 (m, 6H), 2.42 (s, 3H), 3.72 (s, 3H), 3.73 (s, 3H), 4.05 (dd, $J_1 = 6.4$ Hz, $J_2 = 4.0$ Hz, 1H), 4.13 (br, 1H), 4.40 (dd, $J_1 = 13.9$ Hz, $J_2 = 8.7$ Hz, 1H), 4.51 (dd, $J_1 = 13.9$ Hz, $J_2 = 8.3$ Hz, 1H), 5.11 (d, $J = 6.8$ Hz, 1H), 6.55 (br, 1H), 7.15 (d, $J = 8.3$ Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.75 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.57$, 21.67, 21.83, 22.67, 22.78, 24.74, 24.82, 40.66, 41.20, 50.59, 51.24, 52.34, 52.46, 57.07, 70.44, 127.30, 129.87, 136.24, 144.16, 170.54, 170.88, 172.48, 172.70 ppm; IR (KBr): $\tilde{\nu} = 3358$, 3298, 2958, 2872, 1745, 1655, 1533, 1439, 1346, 1165, 1092, 816, 667, 555 cm^{-1}; MS (EI): m/z (%): 556.2 $[M]^+$, 542.2 (30), 526.2 (15), 498.2 (10), 480.2 (1), 438.2 (0), 413.1 (5), 395.1 (3), 385.1 (55), 353.1 (5), 325.1 (20), 297.1 (5), 231.1 (15), 214.1 (60), 203.1 (85), 201.1 (100), 169.1 (5), 157.0 (25), 155.0 (40), 146.1 (25), 139.0 (20), 91.1 (30), 86.1 (35), 69.1 (5), 60.1 (10); HRMS: m/z calcd for $C_{24}H_{36}N_3O_7S$: 542.2172 $[M^+ - CH_3]$; found: 542.2173.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylisobutylmethyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)succinic diamide (5c)**: $[\alpha]_D^{23} = -7$ ($c = 0.5$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (m, 12H), 1.58 (m, 6H), 2.39 (s, 3H), 3.69 (s, 3H), 3.69 (s, 3H), 4.02 (dd, $J_1 = 8.3$ Hz, $J_2 = 3.8$ Hz, 1H), 4.31 (dd, $J_1 = 9.4$ Hz, $J_2 = 3.8$ Hz, 1H), 4.38 (m, 1H), 4.47 (dd, $J_1 = 14.1$ Hz, $J_2 = 8.7$ Hz, 1H), 4.83 (d, $J = 8.3$ Hz, 1H), 6.51 (d, $J = 9.4$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 1H), 7.28 (d, $J = 7.9$ Hz, 2H), 7.35 (d, $J = 8.2$ Hz, 1H), 7.77 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.49$, 21.59, 21.81, 22.68, 22.70, 24.62, 24.63, 40.47, 41.13, 50.46, 51.07, 52.26, 52.37, 56.70, 71.20, 127.12, 129.93, 136.72, 143.93, 170.49, 171.66, 172.32, 172.49 ppm; IR (KBr): $\tilde{\nu} = 3373$, 3317, 2958, 2872, 1743, 1662, 1533, 1439, 1340, 1163, 1091, 810, 671, 559 cm^{-1}; MS (EI): m/z (%): 556.2 $[M]^+$, 542.2 (20), 526.2 (15), 498.2 (5), 480.2 (1), 466.2 (0), 438.2 (0), 413.1 (3), 395.1 (2), 385.1 (30), 353.1 (5), 335.1 (1), 325.1 (15), 295.1 (3), 231.1 (15), 214.1 (40), 203.1 (80), 201.1 (100), 169.1 (5), 157.0 (20), 155.0 (30), 146.1 (20), 139.0 (15), 112.1 (2), 102.0 (2), 91.1 (20), 86.1 (25), 60.1 (10); HRMS: m/z calcd for $C_{24}H_{36}N_3O_7S$: 542.2173 $[M^+ - CH_3]$; found: 542.2172.

***N*,*N*′-Bis[(*S*)-1-methoxycarbonylisopropylmethyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)succinic diamide (5d) and *N*,*N*′-bis[(*S*)-1-methoxycarbonylisopropylmethyl]-(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4d)**: Compound **4d** was synthesized according to general procedure B. The isomers were separated by using flash chromatography and preparative HPLC.

Stereoisomer 1: $[\alpha]_D^{23} = +8$ ($c = 0.50$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (m, 12H), 2.15 (m, 2H), 2.40 (s, 3H), 3.71 (s, 3H), 3.72 (s, 3H), 4.20 (m, 2H), 4.25 (dd, $J_1 = 9.1$ Hz, $J_2 = 4.9$ Hz, 1H), 4.40 (dd, $J_1 = 8.7$ Hz, $J_2 = 4.9$ Hz, 1H), 5.10 (d, $J = 6.6$ Hz, 1H), 6.53 (d, $J = 7.4$ Hz, 1H), 7.26 (m, 3H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.72 ppm (dt, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.51$, 17.67, 18.74, 18.83, 21.48, 26.90, 30.77, 31.06, 52.11, 52.25, 56.95, 57.11, 57.65, 70.66, 127.21, 129.76, 136.31, 144.03, 170.43, 170.86, 171.42, 171.55 ppm; IR (KBr): $\tilde{\nu} =$ 3411, 3355, 3293, 2966, 2879, 1742, 1675, 1527, 1450, 1337, 1276, 1214, 1158, 1096, 671, 554 cm^{-1}; MS (EI): m/z (%): 529.3 $[M]^+$, 498.3 (15), 480.2 (15), 470.3 (10), 399.2 (5), 371.1 (80), 339.1 (5), 311.1 (35), 281.1 (3), 217.2 (20), 214.1 (80), 201.1 (5), 189.1 (100), 187.1 (100), 157.1 (30), 155.0 (40), 139.0 (20), 132.1 (25), 130.1 (20), 127.1 (15), 115.1 (3), 98.1 (8), 91.1 (45), 72.1 (40), 60.1 (15), 55.1 (8); HRMS: m/z calcd for $C_{23}H_{35}N_3O_9S$: 529.2094; found: 529.2106.

Stereoisomer 2: $[\alpha]_D^{23} = -9$ ($c = 0.50$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 7.0$ Hz, 6H), 0.85 (d, $J = 7.0$ Hz, 6H), 2.10 (m, 2H), 2.40 (s, 3H), 3.70 (s, 3H), 3.71 (s, 3H), 3.88 (dd, $J_1 = 9.3$ Hz, $J_2 = 4.0$ Hz, 1H), 4.22 (dd, $J_1 = 9.3$ Hz, $J_2 = 4.0$ Hz, 1H), 4.32 (dd, $J_1 = 8.9$ Hz, $J_2 = 5.1$ Hz, 1H), 4.35 (dd, $J_1 = 9.2$ Hz, $J_2 = 5.1$ Hz, 1H), 5.05 (d, $J = 9.2$ Hz, 1H), 6.72 (d, $J = 9.2$ Hz, 1H), 7.22 (d, $J = 9.2$ Hz, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.40 (d, $J = 8.9$ Hz, 1H), 7.77 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.62$, 18.75, 18.79, 21.49, 30.85, 31.08, 52.14, 52.22, 56.51, 56.85, 57.54, 70.89, 127.10, 130.01, 136.65, 144.15, 170.98, 171.01, 171.43, 172.22 ppm; IR (KBr): $\tilde{\nu} = 3406$, 3305, 2964, 2877, 1741, 1660, 1531, 1437, 1344, 1269, 1211, 1165, 1092, 667, 555 cm^{-1}; MS

(EI): *m/z* (%): 530.2 $[M]^+$, 498.2 (20), 480.2 (20), 470.2 (5), 399.1 (5), 371.1 (40), 342.1 (3), 311.1 (20), 217.1 (10), 214.1 (50), 201.1 (2), 189.1 (100), 187.1 (100), 157.0 (25), 155.0 (30), 132.1 (20), 130.1 (10), 115.1 (2), 98.0 (5), 91.0 (25), 72.1 (25), 60.1 (10); HRMS: *m/z* calcd for $C_{21}H_{32}N_3O_7S$: 470.1961; found: 470.1960.

***N,N'*-Bis[(*S*)-1-methoxycarbonyl-2,2-dimethylpropyl]-(2*S*,3*S*)-3-hydroxy-2-(tosylamino)succinic diamide (5e) and *N,N'*-bis[(*S*)-1-methoxycarbonyl-2,2-dimethylpropyl]-(2*R*,3*R*)-3-hydroxy-2-(tosylamino)succinic diamide (4e)**: Compound **4e** was synthesized according to general procedure B. Separation of the isomers was done by flash chromatography and preparative HPLC.

Stereoisomer 1: $[\alpha]_D^{23} = -6$ ($c = 1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (s, 9H), 0.96 (s, 9H), 2.43 (s, 3H), 3.72 (s, 3H), 3.72 (s, 3H), 4.01 (dd, $J_1 = 8.1$ Hz, $J_2 = 4.3$ Hz, 1H), 4.13 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.3$ Hz, 1H), 4.22 (d, $J = 9.4$ Hz, 1H), 4.29 (d, $J = 9.1$ Hz, 1H), 5.05 (d, $J = 8.1$ Hz, 1H), 6.62 (d, $J = 7.8$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 9.4$ Hz, 1H), 7.77 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.57$, 26.49, 26.52, 34.66, 34.75, 51.87, 51.95, 56.29, 60.10, 60.75, 70.32, 127.20, 130.04, 136.29, 144.34, 170.38, 170.63, 170.70, 171.33 ppm; IR (KBr): $\tilde{\nu} = 3412$, 2966, 2910, 2875, 1741, 1666, 1525, 1437, 1344, 1221, 1163, 1092, 816, 667, 550 cm^{-1}; MS (EI): *m/z* (%): 558.3 $[M]^+$, 542.3 (75), 524.3 (35), 501.3 (30), 498.3 (10), 451.2 (3), 441.2 (10), 395.2 (2), 385.2 (85), 356.2 (5), 325.2 (50), 298.1 (5), 239.1 (5), 231.2 (20), 214.1 (65), 203.2 (100), 201 (95), 171.1 (10), 155.0 (40), 112.1 (10), 98.0 (2), 91.1 (40), 86.1 (60), 69.1 (10), 60.1 (15), 57.1 (10); HRMS: *m/z* calcd for $C_{25}H_{39}N_3O_7S$: 557.2407; found: 557.2427.

Stereoisomer 2: $[\alpha]_D^{23} = -16$ ($c = 0.5$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (s, 9H), 0.93 (s, 9H), 2.44 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.76 (dd, $J_1 = 9.9$ Hz, $J_2 = 4.3$ Hz, 1H), 4.14 (dd, $J_1 = 9.5$ Hz, $J_2 = 4.3$ Hz, 1H), 4.25 (d, $J = 9.9$ Hz, 1H), 4.26 (d, $J = 9.5$ Hz, 1H), 5.14 (d, $J = 9.9$ Hz, 1H), 6.87 (d, $J = 9.5$ Hz, 1H), 7.26 (d, $J = 9.9$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 9.4$ Hz, 1H), 7.78 ppm (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.57$, 26.43, 26.46, 34.59, 51.87, 51.95, 56.30, 59.79, 60.48, 127.14, 130.18, 136.57, 144.38, 170.33, 171.01, 171.17, 172.56 ppm; IR (KBr): $\tilde{\nu} = 3412$, 3358, 3309, 2964, 2873, 1741, 1662, 1529, 1437, 1348, 1221, 1165, 1093, 820, 671, 559 cm^{-1}; MS (EI): *m/z* (%): 558.3 $[M]^+$, 542.3 (35), 524.3 (25), 501.2 (15), 498.3 (5), 441.2 (5), 413.2 (5), 385.2 (40), 356.1 (5), 325.2 (30), 298.1 (2), 231.2 (10), 214.1 (40), 203.1 (80), 201.2 (100), 171.1 (10), 155.0 (25), 146.1 (15), 139.0 (10), 127.0 (2), 112.1 (5), 98.0 (1), 91.1 (25), 86.1 (40), 60.1 (10); HRMS: *m/z* calcd for $C_{25}H_{39}N_3O_7S$: 557.2407; found: 557.2416.

***N*^{4}-[1-Methoxycarbonyl-3-methylbutyl]-*N*^{1}-[1-methoxycarbonylethyl]fumaric diamide (6)**: Compound **6** was synthesized according to general procedure A from *N*-acroyl leucine and *N*-acroyl alanine (1.00 and 1.00 equiv) and was obtained as the as the second fraction and major product from a 2:1:1 mixture by using flash chromatography (EtOAc). The minor products corresponded to the homo-cross-metathesis products and gave identical data as detailed above. The solvent was removed under reduced pressure and the product was isolated by column chromatography (EtOAc).

$[\alpha]_D^{23} = -44$ ($c = 0.3$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (d, $J = 6.2$ Hz, 3H), 0.87 (d, $J = 6.2$ Hz, 3H), 1.32 (d, $J = 7.6$ Hz, 3H), 1.50–1.58 (m, 3H), 3.62 (s, 3H), 3.63 (s, 3H), 4.36–4.47 (m, 2H), 5.60 (br d, $J = 9.0$ Hz, 1H), 6.18 (br d, $J = 10.0$ Hz, 1H), 6.83 (s, 1H), 6.84 ppm (s, 1H); ^{1}H NMR (300 MHz, [D$_4$]methanol): $\delta = 0.94$ (dd, $J_1 = 10.6$ Hz, $J_2 = 6.4$ Hz, 6H), 1.40 (d, $J = 7.4$ Hz, 3H), 1.65 (m, 3H), 3.71 (s, 3H), 3.72 (m, 3H), 4.51 (m, 2H), 6.95 ppm (s, 2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta =$ 17.62, 22.09, 23.48, 26.34, 41.70, 50.04, 52.81, 53.02, 53.09, 134.06, 134.15, 166.52, 166.82, 174.48, 174.55 ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.91$, 20.38, 21.77, 24.63, 39.99, 48.33, 51.10, 51.31, 132.36, 132.45, 164.82, 165.13, 172.79, 172.85 ppm; HRMS: *m/z* calcd for $C_{15}H_{24}N_2O_6$: 328.1634; found: 328.1637.

HPLC characterization of all eight isomers from aminohydroxylation of the three fumaric diamides from metathesis: Chiralcel-OD, *n*-hexane/*tert*-butyl methyl ether, 20:80 (v/v), 1.0 mL min^{-1}; retention times: 14.3 (**4d**), 15.1 (**5d**), 16.3, 16.5, 17.2, 17.9, 18.6 (**4a**), and 19.4 min (**5a**). The peaks between 16.3 and 17.9 min refer to the known products from aminohydroxylation of the asymmetrical substrate.

Aminohydroxylation of the asymmetrical fumaric diamide **6** was carried out following the general procedure B. Analytical data for the four stereoisomers **7a–d** are as follows:

Stereoisomer 1: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.83$ (d, $J = 6.2$ Hz, 3H), 0.85 (d, $J = 6.2$ Hz, 3H), 1.33 (d, $J = 7.2$ Hz, 3H), 1.50–1.56 (m, 3H), 2.35 (s, 3H), 3.64 (s, 3H), 3.66 (s, 3H), 3.97 (dd, $J = 6.9$, 9.2 Hz, 1H), 4.36–4.43 (m, 2H), 4.97 (d, $J = 8.4$ Hz, 1H), 6.56 (d, $J = 9.2$ Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.72 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.97$, 21.46, 21.65, 22.77, 24.57, 41.27, 48.36, 50.38, 52.44, 52.59, 56.74, 70.97, 127.14, 130.00, 136.73, 144.13, 170.44, 171.93, 172.13, 172.54 ppm; HRMS: *m/z* calcd for $C_{22}H_{33}N_2O_9S$: 515.1938; found: 515.1940.

Stereoisomer 2: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (d, $J = 6.2$ Hz, 3H), 0.84 (d, $J = 6.2$ Hz, 3H), 1.34 (d, $J = 7.1$ Hz, 3H), 1.49–1.55 (m, 3H), 2.35 (s, 3H), 3.65 (s, 3H), 3.66 (s, 3H), 3.87 (dd, $J = 6.7$, 9.2 Hz, 1H), 4.29–4.44 (m, 2H), 4.83 (d, $J = 7.1$ Hz, 1H), 6.46 (d, $J = 9.2$ Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 2H), 7.70 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.29$, 21.49, 21.52, 22.77, 24.61, 40.37, 47.84, 51.03, 52.35, 52.51, 56.42, 71.08, 127.17, 129.94, 136.67, 144.03, 170.54, 171.50, 172.36, 172.56 ppm; HRMS: *m/z* calcd for $C_{22}H_{33}N_2O_9S$: 515.1938; found: 515.1951.

Stereoisomer 3: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (d, $J = 6.2$ Hz, 3H), 0.86 (d, $J = 6.2$ Hz, 3H), 1.32 (d, $J = 7.1$ Hz, 3H), 1.52–1.57 (m, 3H), 2.35 (s, 3H), 3.66 (s, 3H), 3.66 (s, 3H), 4.13–4.40 (m, 3H), 5.05 (d, $J = 6.4$ Hz, 1H), 6.52 (d, $J = 9.2$ Hz, 1H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.71 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.52$, 21.53, 21.72, 22.59, 24.75, 41.11, 47.89, 51.29, 52.43, 52.60, 57.40, 71.07, 127.10, 129.80, 136.44, 143.71, 170.35, 171.46, 172.81, 173.04 ppm; HRMS: *m/z* calcd for $C_{22}H_{33}N_2O_9S$: 515.1938; found: 515.1942.

Stereoisomer 4: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.77$ (d, $J = 6.1$ Hz, 3H), 0.86 (d, $J = 6.1$ Hz, 3H), 1.33 (d, $J = 7.1$ Hz, 3H), 2.87 (dd, $J = 6.7$, 9.2 Hz, 3H), 4.15–4.48 (m, 3H), 5.10 (d, $J = 6.6$ Hz, 1H), 6.47 (d, $J = 9.2$ Hz, 1H), 7.24 (d, $J = 8.2$ Hz, 2H), 7.70 ppm (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.27$, 21.55, 21.69, 22.63, 24.26, 40.46, 48.53, 50.53, 52.44, 52.61, 57.45, 70.78, 127.29, 129.77, 136.97, 143.68, 170.61, 171.32, 172.91, 173.16 ppm; HRMS: *m/z* calcd for $C_{22}H_{33}N_2O_9S$: 515.1938; found: 515.1939.

X-ray structure analysis

Compound 4c: $C_{25}H_{39}N_3O_9S \cdot 0.25$ acetone: colorless crystals, crystal dimensions $0.10 \times 0.30 \times 0.50$ mm^3, $M_r = 572.17$, monoclinic, space group $P2_1$ (no. 4), $a = 15.0198(3)$, $b = 27.4936(7)$, $c = 15.0819(4)$ Å, $\beta = 102.355(2)°$, $V = 6083.8(3)$ Å^3, $Z = 8$, $\mu(Mo_{K\alpha}) = 0.159$ mm^{-1}, $T = 123(2)$ K, $F(000) = 2448$. A total of 44665 reflections were measured up to $2\theta_{max} = 50°$ on a Nonius Kappa CCD diffractometer with $Mo_{K\alpha}$ radiation, 20236 of which were independent and used for all calculations. The structure was solved by direct methods and refined to F^2 anisotropically, the hydrogen atoms were refined with a riding model. The final quality coefficient $wR_2(F^2)$ for all data was 0.2235, with a conventional $R(F) = 0.0866$ for 1393 parameters and 21 restraints. The absolute configuration was determined by refinement of Flack's x-parameter ($X = 0.10(9)$).

CCDC-276677 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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