## Synthetic Studies Toward (+)-Spongidepsin

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A convergent enantiomerically controlled synthetic effort toward (+)-spongidepsin is reported. The synthesis benefits from the use of readily available and inexpensive starting materials like D-mannitol and (-)- $\beta$ -citronellene. Key transformations include *Evans* asymmetric methylation, *Mitsunobu* esterification, (1H-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP)-mediated amide formation for the preparation of a fully functionalized acyclic precursor, and ring-closing metathesis (RCM).

**Introduction.** – Marine organisms have been a rich source of biologically active cyclic peptides with unique structural features. (–)-Spongidepsin is a macrolide isolated from a *Spongia* species, collected from the Vanuatu Islands, Australia, by *Riccio* and co-workers [1], with cytotoxic and antiproliferative activities against J774.A1, WEHI-164, and HEK-293 cancer cell lines. (–)-Spongidepsin is a 13-membered macrolactam with five stereogenic centers. Its structure was established by spectroscopic analysis, and the *N*-methylphenylalanine residue with L configuration has been identified by isolation. The absolute configurations at the other four stereogenic centers were determined by total synthesis [2]. While biological studies are severely limited by the scarcity of these natural products, the unprecedented structural features and remarkable biological activity have provided the impetus for additional total syntheses [3]. In continuation of our synthesis work on bioactive macrolides [4], we present herein an enantioselective synthesis of the unnatural (+)-spongidepsin (1).

**Results and Discussion.** – We report here a highly convergent synthesis of (+)-spongidepsin (1) using a ring-closing metathesis (RCM) to from the 13-membered macrocycle [2][3]. In analogy to the described syntheses of the natural (-)-spongidepsin, we envisioned in our retrosynthetic analysis the preparation of three nonracemic components, 3-5, for the convergent assembly of the target macrolactam (*Scheme 1*).

Efforts towards the construction of fragment **4** started with the inexpensive and readily available D-mannitol (**7**; *Scheme 2*), which was converted to the  $\alpha,\beta$ -unsaturated ester **9** by a known procedure [5]. The alkene **9** was reduced selectively with NiCl<sub>2</sub>/NaBH<sub>4</sub> [6] to give the saturated ester **10** in 97% yield, and this was subsequently hydrolyzed to give acid **11**, which was coupled with the *Evans* oxazolidinone (*R*)-4-benzyloxazolidin-2-one ((*R*)-**20**), by forming the activated ester with pivaloyl chloride [7], leading to imide **12** in 75% yield. Asymmetric methylation of

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12 according to the *Evans* protocol (NaHMDS, THF,  $-78^{\circ}$ , and then MeI) [8] afforded 13 in 86% yield as a single stereoisomer. The optimal conditions entailed dropwise addition of 3 equiv. of MeI over 30 min, and the temperature was kept at -78 for 4 h to minimize the formation of the  $\alpha$ -dimethylated by-product. Reductive removal [9] of the chiral auxiliary by treatment with LiBH<sub>4</sub> furnishedthe primary alcohol 14 in 83% yield. This alcohol was converted to its pivalate [10] with 2,2-dimethylpropanoyl chloride (pivaloyl chloride; PivCl) and pyridine in CH<sub>2</sub>Cl<sub>2</sub>, and the crude pivalate was exposed to *Dowex 50WX8* in MeOH to afford diol 15 in 80% yield. The latter was converted to epoxide 16 as described in [11] (NaH, 1-tosyl-1*H*-imidazole) in good yield (96%). Opening of epoxide 16 with the acetylide anion, derived from benzyl propargyl ether, under *Yamaguchi* conditions [12] gave 17. Removal of the Piv group in 17 with DIBAL, followed by oxidation of 18 with PhI(OAc)<sub>2</sub> and TEMPO [13], gave lactone 19 in 92% yield, which was then reduced with DIBAL-H and olefinated by the *Wittig* reaction to give 4 in 73% yield (two steps).

Construction of the acid **5** started with commercially available (-)- $\beta$ -citronellene (**8**), which, *via* the reported ozonolysis [14], furnished the known aldehyde, which, on exposure to *Jones* oxidation [15], gave acid **21** in 85% yield. Coupling of **21** with (*S*)-4-benzyloxazolidin-2-one ((*S*)-**20**) (PivCl, Et<sub>3</sub>N, THF,  $-20^{\circ}$ ; then LiCl, (*S*)-**20**, room temperature) furnished imide **22** in 72% yield. Asymmetric methylation of **22** according to the *Evans* protocol (NaHMDS, THF,  $-78^{\circ}$ ; then MeI, -78 to  $-40^{\circ}$ ) afforded **23** in 80% yield as an 8:2 mixture of diastereoisomers (<sup>1</sup>H-NMR). Reductive removal of the chiral auxiliary by treatment with NaBH<sub>4</sub> [16] gave **24**, which, on further treatment with *Jones* reagent, provided the desired acid **5** (*Scheme 3*).

The amino acid moiety **3** was synthesized in analogy to [2] from the unnatural amino acid D-phenylalanine (6). Boc Protection with  $(Boc)_2O$  in 20% aq. NaOH in



a) NiCl<sub>2</sub>·H<sub>2</sub>O, NaBH<sub>4</sub>, MeOH, 0°, 1 h; 97%. b) LiOH, THF/H<sub>2</sub>O/MeOH 4:4:2, 0° to r.t., 10 h; 91%. c) Pivaloyl chloride (PivCl), Et<sub>3</sub>N, LiCl, *Evans* oxazolidinone (*R*)-**20**, 0°, 4 h; 75%. d) Sodium bis-(trimethylsilyl)amide (NaHMDS), MeI, THF,  $-78^{\circ}$ , 3 h; 86%. e) LiBH<sub>4</sub>, MeOH, Et<sub>2</sub>O,  $-10^{\circ}$ , 1 h; 83%. f) 1. PivCl, pyridine, 4-(dimethylamino)pyridine (DMAP; cat.), CH<sub>2</sub>Cl<sub>2</sub>, 0° to r.t., 2 h; 2. *Dowex* 50WX8, MeOH, r.t., 48 h; 80% (2 steps). g) NaH, 1-tosyl-1*H*-imidazole, THF, 0°, 1.5 h; 96%. h) Benzyl propargyl ether (HCCCH<sub>2</sub>OCH<sub>2</sub>Ph), BuLi, THF,  $-78^{\circ}$ , BF<sub>3</sub>·OEt<sub>2</sub>, 40 min; 93% diisobutylaluminium hydride (DIBAL-H),  $-78^{\circ}$ , 40 min; 90%. j) (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), PhI(OAc)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> + H<sub>2</sub>O 1:1, r.t., 3 h; 92%. k) 1. DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>,  $-78^{\circ}$ , 30 min; 2. Ph<sub>3</sub>P(Me)<sub>3</sub>I, NaHMDS,  $-78^{\circ}$  to 0°, 5 h; 73% (2 steps).

THF afforded *N*-Boc-D-phenylalanine (**25**) in 90% yield, which was *N*-methylated [17] with NaH and MeI in THF at  $0^{\circ}$  to room temperature to give compound **3** as two rotamers in 98% yield (*Scheme 4*).

Having three fragments in our hand, we focused on the completion of the synthesis of (+)-spongidepsin as outlined in *Scheme 5*. A *Mitsunobu* esterification (Ph<sub>3</sub>P, diisopropyl azodicarboxylate, Et<sub>2</sub>O, room temperature) [18] of **3** with the secondary alcohol **4** led to **26** containing minor amounts of isomers. After separation by flash





a) 1. O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, then Me<sub>2</sub>S, -78°, 30 min; 88%; 2. Jones oxidation, acetone, 0°, 2 h; 85%. b) PivCl, Et<sub>3</sub>N, LiCl, Evans oxazolidinone (S)-20, 0°, 4 h; 72%. c) NaHMDS, MeI, THF, -78°, 3 h; 80%. d) NaBH<sub>4</sub>, THF/H<sub>2</sub>O (5:1), 0° to r.t., 12 h; 80%. e) Jones oxidation, acetone, 0°, 1 h; 86%.



a) (Boc)<sub>2</sub>O, 20% NaOH, THF; 90%. b) NaH, MeI, THF, 0° to r.t., 12 h; 98% (in [2]).

chromatography on SiO<sub>2</sub>, **26** was isolated in 65% yield. Removal of the Boc protecting group by treatment with TFA (CH<sub>2</sub>Cl<sub>2</sub>, room temperature) [19] afforded the free amine **27**, which was coupled with the unsaturated acid **5** by using PyBOP and DIPEA in CH<sub>2</sub>Cl<sub>2</sub> [20] to furnish diene **28** in 70% yield (overall yield for the two steps). RCM of this diene **28** using second-generation *Grubbs* catalyst, **29**, was attempted as reported in [2][3], but unfortunately we were unable to obtain cyclized product under a variety of RCM conditions (*Table*).

Table. Reaction Conditions for RCM

Entry	Catalyst	mol-%	Solvent	Temp. [°]	Time [h]	Outcome	Recovered 28 [%]
1	29	15	$CH_2Cl_2$	40	20	No reaction	95
2	29	15	Toluene	100	12	No reaction	90
3	29	50	$CH_2Cl_2$	40	20	No reaction	60
4	29	50	Toluene	100	12	No reaction	40
5	30	10	$CH_2Cl_2$	40	16	No reaction	80
6	30	40	Toluene	100	10	No reaction	40

Then, assuming that the C $\equiv$ C bond may be creating problems due to the linearity of the system, which may prevent RCM, we blocked the C $\equiv$ C bond by using [Co<sub>2</sub>(CO)<sub>6</sub>] [21] and with the cobalt compound **31**, and we investigated the RCM [22] by using catalyst **29** and obtained the Co-free ring-closed product **32** (*Scheme 6*).



*a*) Ph<sub>3</sub>P, Diisopropyl azodicarboxylate, THF, 0° to r.t., 10 h; 65%. *b*) CF<sub>3</sub>COOH (TFA), CH<sub>2</sub>Cl<sub>2</sub>, 0°, 3 h; 90%. *c*) (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), Et-N( $^{\circ}$ Pr)<sub>2</sub> (DIPEA), acid **5**, CH<sub>2</sub>Cl<sub>2</sub>, 0° to r.t., 12 h; 70%.



*a*) [(Co)<sub>2</sub>(CO)<sub>8</sub>], Toluene, r.t., 30 min; 90%. *b*) Second-generation *Grubbs* catalyst (**29**; 30 mol-%), toluene, reflux, 10 h; 30%.

In summary, we have developed an efficient, and highly enantio- and diastereoselective route for the synthesis of **32**, starting from simple and commercially available chiral materials such as D-mannitol and (-)- $\beta$ -citronellene. Key steps involved in this synthesis are the *Evans* asymmetric methylation, *Mitsunobu* esterification, PyBOPmediated amide formation (for the formation of a fully functionalized acyclic precursor), and ring-closing metathesis. Extension of the above strategy to a total synthesis of spongidepsin and structural activity investigation is currently underway in our laboratory.

## **Experimental Part**

*General.* All commercially available reagents were used without further purification unless otherwise stated. The solvents used were all of anal.-reagent grade and were distilled under N<sub>2</sub> where necessary. All reactions were performed in pre-dried apparatus under N<sub>2</sub> unless otherwise stated. The progress of the reactions was monitored by anal. TLC performed on *Merck* Silica Gel  $60F_{254}$  plates. Visualization was performed using 5% H<sub>2</sub>SO<sub>4</sub> soln. followed by heating. Column chromatography (CC): silica gel 60-120 mesh (SiO<sub>2</sub>; *Qingdao Marine Chemical*, P. R. China). Yields were of purified compounds and were not optimized. Optical rotations: *JASCO DIP 300* digital polarimeter at 25°. NMR Spectra: *Bruker* 300 MHz spectrometers, with TMS as an internal standard, in CDCl<sub>3</sub>, the chemical shifts in ppm; and the coupling constants, *J*, in Hz. High-resolution (HR) MS: *LC-MSD-Trap-SL* instrument.

*Ethyl 3-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]propanoate* (**10**). NiCl<sub>2</sub> · 6 H<sub>2</sub>O (4.9 g, 20.97 mmol) and then portionwise NaBH<sub>4</sub> (3.24 g, 85.8 mmol) were added to a stirred soln. of the unsaturated ester **9** (10.0 g, 41.3 mmol) in MeOH (100 ml) at 0°. After 1 h, the solvent was evaporated, and the residue was filtered through *Celite* using Et<sub>2</sub>O as an eluent (60 ml). The org. phase was concentrated, and the residue was purified by FCC (AcOEt/hexane 1:9) to yield 9.76 g of **10** (97%). Colorless oil.  $[\alpha]_D^{25} = -4.6$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 2938, 2862, 1735, 1148, 1219, 1164, 1105, 1037, 771. <sup>1</sup>H-NMR: 4.09 – 3.99 (m, 3 H); 3.94 (t, J = 7.5, 1 H); 3.45 (t, J = 7.5, 1 H); 2.44 – 2.22 (m, 2 H); 1.85 – 1.70 (m, 2 H); 1.58 – 1.40 (m, 8 H); 1.35 – 1.23 (m, 2 H); 1.16 (t, J = 6.7, 3 H). <sup>13</sup>C-NMR: 172.8; 109.1; 74.3; 68.4; 60.0; 36.3; 34.9; 30.2; 28.6; 24.9; 23.7; 23.5; 13.9. ESI-MS: 265 ( $[M + Na]^+$ ). HR-MS: 265.1420 ( $[M + Na]^+$ , C<sub>13</sub>H<sub>22</sub>NaO<sub>4</sub>; calc. 265.1416).

3-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl)propanoic Acid (11). To a stirred soln. of 10 (5 g, 20.6 mmol) in THF (20 ml), H<sub>2</sub>O (20 ml), and MeOH (10 ml) was added LiOH (0.715 g, 30.976 mmol), and the mixture was stirred at r.t. for 10 h. After completion of the reaction (TLC), the mixture was extracted with Et<sub>2</sub>O, the aq. layer was acidified to pH 2 with 2N HCl, and extracted with AcOEt (4 × 40 ml). The combined org. layer was washed with brine (40 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Purification of the crude product by CC (SiO<sub>2</sub>; AcOEt/hexane, 4 :6) afforded 11 (4.02 g, 91%). Colorless oil.  $[a]_{25}^{25} = -6.6 (c = 1, CHCl_3)$ . <sup>1</sup>H-NMR: 4.16–3.98 (*m*, 2 H); 3.56–3.48 (*m*, 1 H); 2.58–2.38 (*m*, 2 H); 1.95–1.75 (*m*, 2 H); 1.63–1.51 (*m*, 10 H). <sup>13</sup>C-NMR: 179.2; 109.6; 74.3; 68.5; 36.6; 35.1; 30.2; 28.6; 25.1; 23.9; 23.8. ESI-MS: 237 ( $[M + Na]^+$ ). HR-MS: 237.1107 ( $[M + Na]^+$ , C<sub>11</sub>H<sub>18</sub>NaO<sub>4</sub><sup>+</sup>; calc. 237.1103).

(4R)-4-Benzyl-3-[3-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]propanoyl]-1,3-oxazolidin-2-one (12). To a soln. of **11** (4 g, 18.6 mmol) in THF (90 ml) were added Et<sub>3</sub>N (6.5 ml, 46.8 mmol) and PivCl (1.59 ml, 18.6 mmol) in sequence at  $-20^{\circ}$ . After stirring for 1 h, LiCl (1.19 g, 28.2 mmol) and (*R*)-**20** (3.31 g, 18.6 mmol) were added. The mixture was stirred for 1 h at  $-20^{\circ}$  and warmed to  $0^{\circ}$ . After stirring for 4 h at  $0^{\circ}$ , the reaction was quenched by addition of sat. NH<sub>4</sub>Cl soln. (30 ml). The resulting mixture was extracted with Et<sub>2</sub>O (2 × 50 ml). The combined org. extracts were washed with brine (50 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated. FCC (hexane/AcOEt 8:2) provided **12** (5.2 g, 75%). [ $\alpha$ ]<sup>25</sup>/<sub>25</sub> = -43.3 (c = 1, CHCl<sub>3</sub>). IR (KBr): 3383, 2934, 1782, 1700, 1449, 1387, 1214, 1102, 765. <sup>1</sup>H-NMR: 7.39 – 7.13 (m, 5 H); 4.65 – 4.54 (m, 1 H); 4.20 – 4.08 (m, 3 H); 4.03 (t, J = 8.3, 1 H); 3.55 (t, J = 8.3, 1 H); 3.37 – 3.27 (m, 1 H); 3.11 – 2.94 (m, 2 H); 2.77 – 2.64 (m, 1 H); 1.90 (dd, J = 6.7, 14.4, 2 H); 1.63 – 1.50 (m, 8 H); 1.44 – 1.33 (m, 2 H). <sup>13</sup>C-NMR: 172.3; 152.9; 135.4; 129.4; 129.0; 127.3; 109.4; 74.5; 68.8; 65.9; 55.2; 38.1; 36.8; 35.3; 31.9; 28.4; 25.3; 24.0; 23.9. ESI-MS: 396 ([M + Na]<sup>+</sup>). HR-MS: 396.1783 ([M + Na]<sup>+</sup>, C<sub>21</sub>H<sub>27</sub>NNaO<sup>+</sup><sub>5</sub>; calc. 396.1787).

(4R)-4-Benzyl-3-[(2R)-3-[(2S)-1,4-dioxaspiro[4.5]dec-2-yl]-2-methylpropanoyl]-1,3-oxazolidin-2one (13). NaHMDS (1.0m soln. in THF, 16 ml, 16 mmol) was added to a soln. of 12 (4 g, 10.7 mmol) in THF (42 ml) at  $-78^{\circ}$ . After stirring for 30 min, MeI (1.98 ml, 32.1 mmol) was added. This mixture was stirred at  $-78^{\circ}$  for 3 h, and then treated with sat. NH<sub>4</sub>Cl soln. (20 ml) and extracted with Et<sub>2</sub>O (2 × 50 ml). The combined org. extracts were washed with brine (50 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was purified by FCC (hexane/AcOEt 85 :15) to give 13 (3.56 g, 86%). [ $\alpha$ ] $_{25}^{D}$  = -66.9 (c = 1, CHCl<sub>3</sub>). IR (KBr): 3451, 2934, 2858, 1781, 1697, 1452, 1386, 1215, 1102, 1037, 762. <sup>1</sup>H-NMR: 7.38 -7.18 (m, 5 H); 4.68 - 4.59 (m, 1 H); 4.23 - 4.13 (m, 2 H); 4.11 - 4.04 (m, 1 H); 4.02 - 3.97 (m, 1 H); 3.94 - 3.84 (m, 1 H); 3.51 (t, J = 6.9, 1 H); 3.33 - 3.27 (m, 1 H); 2.78 - 2.72 (m, 1 H); 2.08 - 2.00 (m, 1 H); 1.71 - 1.64 (m, 1 H); 1.61 - 1.50 (m, 8 H); 1.43 - 1.35 (m, 2 H); 1.29 (d, J = 6.9, 3 H). <sup>13</sup>C-NMR: 176.3; 152.7; 135.2; 129.4; 128.9; 127.3; 109.4; 73.5; 69.0; 66.0; 55.3; 37.9; 36.8; 36.7; 35.2; 34.9; 25.1; 24.0; 23.8; 18.1. ESI-MS: 410 ( $[M + Na]^+$ ). HR-MS: 410.1949 ( $[M + Na]^+$ , C<sub>22</sub>H<sub>29</sub>NNaO<sup>‡</sup>; calc. 410.1943).

(2R)-3-[(2S)-1,4-Dioxaspiro[4.5]dec-2-yl]-2-methylpropan-1-ol (14). LiBH<sub>4</sub> (2.0M soln. in THF, 22.6 ml, 45.2 mmol) was dropwise added to a soln. of 13 (3.5 g, 9.0 mmol) and MeOH (0.93 ml, 16.0 mmol) in Et<sub>2</sub>O (16 ml) at  $-10^{\circ}$ . After stirring for 1 h at  $-10^{\circ}$ , the resulting mixture was treated with 1N NaOH soln. (28 ml), stirred for 20 min at 0°, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 70 ml). The combined org. extracts were washed with brine (40 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was purified by flasch CC (hexane/AcOEt 75:25) to give 14 (1.6 g, 83%).  $[a]_{25}^{25} = +2.2$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3384, 2935, 2871, 1219, 1037, 772. <sup>1</sup>H-NMR: 4.26–4.14 (m, 1 H); 4.08–4.02(m, 1 H); 3.57–3.42 (m, 3 H); 2.91 (s, 1 H); 1.90–1.76 (m, 1 H); 1.69–1.51(m, 10 H); 1.44–1.34 (m, 2 H); 0.98 (d, J = 6.8, 3 H). <sup>13</sup>C-NMR: 109.2; 73.4; 69.2; 67.1; 37.1; 36.6; 35.2; 33.1; 25.1; 24.0; 23.8; 23.7; 16.8. ESI-MS: 237 ( $[M + Na]^+$ ). HR-MS: 237.1459 ( $[M + Na]^+$ , C<sub>12</sub>H<sub>22</sub>NaO<sub>3</sub><sup>+</sup>; calc. 237.1467).

(2R,4S)-4,5-Dihydroxy-2-methylpentyl 2,2-Dimethylpropanoate (15). To a cooled 0° soln. of 14 (2.5 g, 11.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml) were successively added pyridine (9.3 ml, 116 mmol), PivCl (2.8 ml, 23.2 mmol), and DMAP (70 mg, 0.58 mmol). The mixture was allowed to warm to r.t. and stirred for 2 h. H<sub>2</sub>O was added, and the resulting soln. was extracted with Et<sub>2</sub>O. The extracts were washed with H<sub>2</sub>O and brine, then dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give the corresponding crude pivalate, which was used in the next step without further purification.

To a soln. of the crude pivalate (3.40 g) in MeOH (113 ml) was added *Dowex 50WX8* (16 g). After stirring for 48 h at r.t., the mixture was basicified with Et<sub>3</sub>N (6 ml). The resulting mixture was filtered through a *Celite* pad eluting with MeOH, and the filtrate was extracted with hexane (3 ×, to remove 1,1-dimethoxycyclohexane). The MeOH layer was concentrated under reduced pressure to give a yellow oil. The oil was dissolved in dry toluene (5 ml), and the solvent was removed *in vacuo* (azeotropic MeOH removal) to give **15** (2.03 g, 80%).  $[\alpha]_{25}^{25} = -9.2$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3379, 2965, 2935, 1725, 1462, 1287, 1186, 1033, 772. <sup>1</sup>H-NMR: 4.08–3.99 (*m*, 1 H); 3.95–3.86, (*m*, 1 H); 3.80 (*s*, 1 H); 3.67–3.56 (*m*, 1 H); 3.47–3.29 (*m*, 1 H); 3.16 (*s*, 1 H); 1.20–1.95 (*m*, 1 H); 1.45–1.35 (*m*, 1 H); 1.20 (*s*, 9 H); 1.01 (d, J = 6.8, 3 H). <sup>13</sup>C-NMR: 178.8; 69.8; 68.4; 66.7; 38.8; 36.5; 29.3; 27.1; 17.8. ESI-MS: 241 ([M+Na]<sup>+</sup>). HR-MS: 241.1421 ([M+Na]<sup>+</sup>, C<sub>11</sub>H<sub>22</sub>NaO<sup>+</sup><sub>4</sub>; calc. 241.1416).

(2R)-2-*Methyl-3-[*(2S)-*oxiran-2-yl]propyl* 2,2-*Dimethylpropanoate* (**16**). To a soln. of **15** (2 g, 9.17 mmol) in THF (30 ml) at 0° was added NaH (60 wt.-% in mineral oil, 1.0 g, 27.4 mmol). The mixture was then warmed to r.t. and stirred for 40 min. The mixture was then cooled to 0°, 1-tosyl-1*H*-imidazole (3.2 g, 9.6 mmol) was added in one portion, the mixture was allowed to warm to ambient temp., and was stirred for 30 min. The reaction was quenched with H<sub>2</sub>O (30 ml), and the mixture was extracted with Et<sub>2</sub>O ( $3 \times 50$  ml). The combined org. layers were washed with brine (30 ml), dried (anh. MgSO<sub>4</sub>), filtered, and concentrated *in vacuo*. Flash CC (SiO<sub>2</sub>, AcOEt/hexane 10:90) provided **16** (1.75 g, 96% yield). Colorless oil. [a]<sub>25</sub><sup>25</sup> = -11.7 (c = 1, CHCl<sub>3</sub>). IR (KBr): 2967, 2932, 1729, 1480, 1284, 1159, 1033, 772. <sup>1</sup>H-NMR: 3.93 (d, J = 6.0, 2 H); 2.96–2.89 (m, 1 H); 2.77–2.71 (m, 1 H); 2.43–2.38 (m, 1 H); 2.08–1.99 (m, 1 H); 1.64–1.55(m, 1 H); 1.42–1.33 (m, 1 H); 1.17 (s, 9 H); 1.01 (d, J = 70, 3 H). <sup>13</sup>C-NMR: 178.4; 68.4; 50.7; 46.8; 36.4; 31.2; 27.1; 17.2. ESI-MS: 223 ([M+Na]<sup>+</sup>). HR-MS: 223.1312 ([M+Na]<sup>+</sup>, C<sub>11</sub>H<sub>20</sub>NaO<sup>±</sup><sub>3</sub>; calc. 223.1310).

(2R,4S)-8-(Benzyloxy)-4-hydroxy-2-methyloct-6-yn-1-yl 2,2-Dimethylpropanoate (17). To a stirred – 78° soln. of benzyl propargyl ether (2.57 g, 17.5 mmol) in THF (30 ml) was added BuLi (10.3 ml of a 1.60M soln. in hexane, 16.6 mmol). The resulting soln. was stirred for 15 min before being added *via* cannula to a soln. of **16** (1.75 g, 8.7 mmol) in THF (20 ml) at  $-78^{\circ}$ . Freshly dist. BF<sub>3</sub>·Et<sub>2</sub>O (1.25 ml, 8.7 mmol) was added dropwise, and the resulting soln. was stirred at  $-78^{\circ}$  for 40 min, sat. aq. NaHCO<sub>3</sub> (20 ml) was added, and THF was removed by rotary evaporation. The residue was diluted with AcOEt, and the resulting emulsion was filtered under vacuum. The separated aq. residue was extracted with AcOEt (3 × 50 ml), and the combined org. layers were washed with H<sub>2</sub>O and sat. aq. NaCl (75 ml each), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The residue was purified by CC (hexane/AcOEt 80:20) to yield **17** (2.8 g, 93%) as a clear, colorless oil.  $[a]_{25}^{25} = -0.8 (c = 1, CHCl_3)$ . IR (KBr): 3453, 2932, 2237, 1727, 1455, 1219, 1071, 771. <sup>1</sup>H-NMR: 7.38–7.28 (m, 5 H); 4.58 (s, 2 H); 4.19–4.14 (m, 2 H); 4.05–3.85 (m, 3 H); 2.55–2.31 (m, 2 H); 2.10–1.97 (m, 1 H); 1.66–1.39 (m, 2 H); 1.20 (s, 9 H); 1.00 (d, J=6.8, 3 H).

<sup>13</sup>C-NMR: 178.5; 137.3; 128.3; 127.9; 127.8; 83.0; 78.6; 71.5; 68.3; 67.7; 57.5; 39.9; 29.5; 28.1; 27.1; 17.7. ESI-MS: 369 ( $[M + Na]^+$ ). HR-MS: 369.2047 ( $[M + Na]^+$ , C<sub>21</sub>H<sub>30</sub>NaO<sup>+</sup><sub>4</sub>; calc. 369.2042).

(2R,4S)-8-(Benzyloxy)-2-methyloct-6-yne-1,4-diol (18). To a cooled  $(-78^{\circ})$  soln. of 17 (2 g, 5.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 ml) was added DIBAL-H (17.3 ml, 17.3 mmol) in hexane (1.0m). After 40 min at  $-7^{\circ}$ , the reaction was quenched with MeOH (16 ml) and sat. aq. *Rochelle* salt (40 ml), and the mixture was stirred at r.t. for 1 h vigorously and extracted with AcOEt (4 × 50 ml). Combined extracts were washed with brine (40 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to give alcohol. Flash CC (SiO<sub>2</sub>, AcOEt/hexane 30:70) gave 18 (1.36 g, 90% yield). Colorless oil.  $[a]_{25}^{25}$  = +4.5 (*c* = 1, CHCl<sub>3</sub>). IR (KBr): 3367, 2925, 2872, 2234, 1714, 1454, 1355, 1261, 1069, 699. <sup>1</sup>H-NMR: 7.40–7.27 (*m*, 5 H); 4.58 (*s*, 2 H); 4.16 (*s*, 2 H); 4.00–3.89 (*m*, 1 H); 3.58–3.40 (*m*, 2 H); 2.47–2.39 (*m*, 2 H); 1.99–1.84 (*m*, 1 H); 1.61 (*t*, *J* = 6.0, 2 H); 0.94 (*d*, *J* = 7.6, 3 H). <sup>13</sup>C-NMR: 162.5; 137.3; 128.3; 127.9; 127.7; 83.8; 77.9; 71.4; 67.4; 57.5; 40.6; 31.9; 27.6; 17.1. ESI-MS: 285 ([*M* + Na]<sup>+</sup>). HR-MS: 285.1458 ([*M* + Na]<sup>+</sup>, C<sub>16</sub>H<sub>22</sub>NaO<sub>3</sub><sup>+</sup>; calc. 285.1467).

(3R,5S)-5-[4-(Benzyloxy)but-2-yn-1-yl]-3-methyldihydrofuran-2(3H)-one (19). To a soln. of 18 (1.3 g, 4.9 mmol) in H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> 1 :1 (20 ml) were added TEMPO (231.5 mg, 1.48 mmol) and PhI(OAc)<sub>2</sub> (4.7 g, 14.7 mmol). After stirring at r.t. for 3 h, the mixture was diluted with CHCl<sub>3</sub> and then washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The org. layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash CC (20% AcOEt/hexane) afforded 19 (1.17 g, 92%). Clear oil.  $[a]_{25}^{25} = +0.7$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 2928, 2854, 2240, 1770, 1715, 1454, 1355, 1261, 1190, 1016, 700. <sup>1</sup>H-NMR: 7.36 – 7.20 (m, 5 H); 4.63 – 4.49 (m, 3 H); 4.08 (s, 2 H); 2.81 – 2.66 (m, 1 H); 2.64 – 2.25 (m, 2 H); 2.41 – 2.29 (m, 1 H); 2.09 – 1.96 (m, 1 H); 1.27 (d, J = 7.6, 3 H). <sup>13</sup>C-NMR: 179.5; 137.2; 128.3; 127.9; 127.8; 80.8; 78.9; 75.2; 71.6; 57.4; 34.2; 33.6; 25.3; 15.9. ESI-MS: 276 ( $[M + NH_4]^+$ ).

(3R,5S)-9-(Benzyloxy)-3-methylnon-1-en-7-yn-5-ol (4). To a soln. of 19 (1 g, 3.87 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> under Ar was added dropwise 1.0M soln. of DIBAL-H (7.75 ml, 7.75 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at  $-78^{\circ}$ . After stirring for 30 min at  $-78^{\circ}$ , the reaction was quenched with 20 ml of MeOH. The resulting mixture was allowed to warm to 23° over 1 h until a white precipitate appeared. The residue was filtered on a pad of *Celite*, washed with Et<sub>2</sub>O, and concentrated to give the crude lactol, which was directly used in the next step.

To a soln. of Ph<sub>3</sub>P(Me)I (6.1 g, 17.6 mmol) in 50 ml of THF under Ar was added 1.6M soln. of NaHMDS (11 ml, 17.6 mmol) in toluene at  $-78^{\circ}$ . After stirring at  $-78^{\circ}$  for 30 min, the crude lactol in 10 ml of THF was added. After stirring for further 5 h at 0°, the reaction was quenched with sat. aq. NH<sub>4</sub>Cl, and the mixture was extracted with Et<sub>2</sub>O, washed with brine, dried (anh. MgSO<sub>4</sub>), and concentrated. Purification by CC (hexane/AcOEt 80:20) gave **4** (730 mg, 73%). Colorless oil.  $[\alpha]_{D}^{25} = -6.6$  (c = 1, CHCl<sub>3</sub>). IR (KBr). 3469, 3071, 2970, 2236, 1720, 1641, 1452, 1261, 1112, 914, 698. <sup>1</sup>H-NMR: 7.31–7.20 (m, 5 H); 5.75–5.54 (m, 1 H); 5.02–4.85 (m, 2 H); 4.51 (s, 2 H); 4.11 (s, 2 H); 3.79–3.69 (m, 1 H); 2.45–2.23 (m, 3 H); 1.62–1.33 (m, 2 H); 0.97 (d, J = 6.7, 3 H). <sup>13</sup>C-NMR: 143.6; 137.4; 128.4; 128.0; 127.8; 113.7; 83.3; 78.4; 71.5; 67.9; 57.6; 43.1; 34.6; 28.2; 21.1. ESI-MS: 276 ([M + NH<sub>4</sub>]<sup>+</sup>). HR-MS: 276.1960 ([M + NH<sub>4</sub>]<sup>+</sup>, C<sub>17</sub>H<sub>26</sub>NO<sub>2</sub><sup>+</sup>; calc. 276.1964).

(4R)-4-Methylhex-5-enoic Acid (21). (-)- $\beta$ -Citronellene (8; 6 g, 43.4 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 ml) and cooled to  $-78^{\circ}$ . O<sub>3</sub> was bubbled through the soln. until a persistent and homogeneous blue color appeared. At this point, N<sub>2</sub> was bubbled instead of O<sub>3</sub> until disappearance of the blue color. Me<sub>2</sub>S (6.4 ml, 86.8 mmol) was then added, and the soln. was allowed to warm to r.t. for 2 h under stirring. Washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated at low temp. under reduced pressure to give aldehyde which was used in the next step without any further purification.

To a soln. of aldehyde in acetone (50 ml) was added *Jones* reagent (4.2 ml) at 0°, and the mixture was stirred at the same temp. for 2 h. <sup>i</sup>PrOH was added, and the resulting mixture was filtered, concentrated *in vacuo*, the residue was dissolved in 30 ml of AcOEt, washed with brine ( $3 \times 5$  ml), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The residue was purified by CC (hexane/AcOEt 75:25) to afford **21** (4.0 g, 85%). Colorless oil. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -6.1 (c = 1, CHCl<sub>3</sub>). <sup>1</sup>H-NMR: 11.36-10.57 (s, 1 H); 5.68-5.58 (m, 1 H); 5.05-4.92 (m, 2 H); 2.41-2.27 (m, 2 H); 2.24-2.11 (m, 1 H); 1.77-1.54 (m, 2 H); 1.02 (d, J = 6.4, 3 H). <sup>13</sup>C-NMR: 180.3; 143.1; 113.8; 37.2; 32.0; 31.2; 19.8.

(4S)-4-Benzyl-3-[(4R)-4-methylhex-5-enoyl]-1,3-oxazolidin-2-one (22). To a soln. of 21 (1.22 g, 5.5 mmol) in THF (28 ml) were added  $Et_3N$  (1.92 ml, 13.8 mmol) and PivCl (0.47 ml, 5.5 mmol) in

sequence at  $-20^{\circ}$ . After stirring for 1 h, LiCl (352 mg, 8.3 mmol) and imide (*S*)-**20** (975 mg, 5.5 mmol) were added. The mixture was stirred for 1 h at  $-20^{\circ}$  and warmed to  $0^{\circ}$ . After stirring for 3 h at  $0^{\circ}$ , the reaction was quenched by addition of sat. NH<sub>4</sub>Cl soln. (10 ml). The resulting mixture was extracted with Et<sub>2</sub>O (2 × 50 ml). The combined org. extracts were washed with brine (30 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated. Flash CC (hexane/AcOEt 8:2) provided **22** (1.51 g, 72%). [*a*]<sub>25</sub><sup>25</sup> = +43.3 (*c*=1, CHCl<sub>3</sub>). IR (KBr): 2962, 2926, 1782, 1699, 1386, 1210, 1098, 703. <sup>1</sup>H-NMR: 7.34–7.12 (*m*, 5 H); 5.77–5.55 (*m*, 1 H); 5.06–4.89 (*m*, 2 H); 4.66–4.53 (*m*, 1 H); 4.13–4.02 (*m*, 2 H); 3.28–3.16 (*m*, 1 H); 2.96–2.65 (*m*, 3 H); 2.28–2.12 (*m*, 1 H); 1.78–1.55 (*m*, 2 H); 1.04 (*d*, *J* = 6.8, 3 H). <sup>13</sup>C-NMR: 172.4; 152.6; 143.0; 135.0; 128.9; 128.3; 126.7; 113.2; 65.5; 54.5; 37.3; 37.0; 32.9; 30.3; 19.8. ESI-MS: 288 ([*M* + H]<sup>+</sup>). HR-MS: 288.1604 ([*M* + H]<sup>+</sup>, C<sub>17</sub>H<sub>22</sub>NO<sub>3</sub><sup>+</sup>; calc. 288.1600).

(4S)-4-*Benzyl-3-[*(2S,4R)-2,4-*dimethylhex-5-enoyl]-1,3-oxazolidin-2-one* (**23**). NaHMDS (1.0M soln. in THF, 6.3 ml, 6.3 mmol) was added to a soln. of **22** (1.62 g, 4.2 mmol) in THF (21 ml) at  $-78^{\circ}$ . After stirring for 30 min, MeI (0.78 ml, 12.6 mmol) was added. This mixture was stirred at  $-78^{\circ}$  for 4 h, and then treated with sat. NH<sub>4</sub>Cl soln. (10 ml) and extracted with Et<sub>2</sub>O (2 × 50 ml). The combined org. extracts were washed with brine (30 ml), dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was purified by flash CC (hexane/acetone 85:15) to give **23** (1.3 g, 80%).  $[a]_{25}^{25} = +57.7$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 2967, 1780, 1696, 1386, 1210, 1100, 702. <sup>1</sup>H-NMR: 7.39-7.16 (m, 5 H); 5.74-5.54 (m, 1 H); 5.04-4.83 (m, 2 H); 4.73-4.53 (m, 1 H); 4.20-4.09 (m, 2 H); 3.85-3.65 (m, 1 H); 3.30-3.17 (m, 1 H); 2.84-2.69 (m, 1 H); 2.30-2.11 (m, 1 H); 1.92-1.75 (m, 1 H); 1.46-1.31 (m, 1 H); 1.21 (d, J = 6.8, 3 H); 1.00 (d, J = 6.8, 3 H). <sup>13</sup>C-NMR: 177.2; 152.8; 143.7; 135.2; 129.3; 128.7; 127.1; 112.9; 65.8; 55.1; 39.8; 37.7; 36.6; 35.9; 35.5; 20.9; 17.6. ESI-MS: 302 ( $[M+H]^+$ ). HR-MS: 302.1759 ( $[M+H]^+$ , C<sub>18</sub>H<sub>24</sub>NO<sub>3</sub><sup>+</sup>; calc. 302.1756).

(2S,4R)-2,4-Dimethylhex-5-en-1-ol (24). To a cooled 0° soln. of 23 (1.2 g, 3.9 mmol) in THF/H<sub>2</sub>O (5:1, 20ml) was added portionwise NaBH<sub>4</sub> (0.67 g, 19.9 mmol). After 10 h at r.t., the reaction was quenched with sat. NH<sub>4</sub>Cl (10 ml), and the mixture was stirred at r.t. for 1 h vigorously and extracted with AcOEt (4 × 10 ml). Combined extracts were washed with brine (20 ml), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. Purification of the product by CC (SiO<sub>2</sub>; hexane/AcOEt 70:30) afforded 24 (411 mg, 80%) Colorless oil.  $[\alpha]_{D}^{25} = -30.2$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3351, 2925, 2856, 1640, 1459, 1219, 1033, 910, 772. <sup>1</sup>H-NMR: 5.64 - 5.54 (m, 1 H); 4.99 - 4.85 (m, 2 H); 3.43 - 3.29 (m, 2 H); 2.96 - 2.85 (m, 1 H); 2.28 - 2.16 (m, 1 H); 1.71 - 1.58 (m, 1 H); 1.41 - 1.23 (m, 2 H); 1.0 (d, J = 7.0, 3 H); 0.88 (d, J = 7.0, 3 H). <sup>13</sup>C-NMR: 144.2; 112.6; 68.1; 40.2; 35.3; 33.1; 21.3; 16.1.

(2S,4R)-2,4-Dimethylhex-5-enoic Acid (5). To a soln. of **24** (400 mg, 3.1 mmol) in acetone (10 ml) was added *Jones* reagent (4.0 ml) at 0°, and the mixture was stirred at the same temp. for 1 h. <sup>i</sup>PrOH was added, and the resulting mixture was filtered, concentrated *in vacuo*, and the residue was dissolved in 30 ml of AcOEt, washed with brine (3 × 5 ml), dried (anh. Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The residue was purified by CC (hexane/AcOEt 80:20) to afford **5** (381 mg, 86%). Colorless oil.  $[a]_D^{25} = +8.5$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3450, 3050, 1707, 1460, 1417, 1243, 914. <sup>1</sup>H-NMR: 5.69–5.54 (*m*, 1 H); 5.04–4.88 (*m*, 2 H); 2.56–2.44 (*m*, 1 H); 2.26–2.13 (*m*, 1 H); 1.79–1.66 (*m*, 1 H); 1.40–1.27 (*m*, 1 H); 1.15 (*d*, J = 6.9, 3 H); 1.01 (d, J = 6.9, 3 H). <sup>13</sup>C-NMR: 183.7; 143.3; 113.5; 39.9; 37.2; 35.7; 20.5; 16.5. EI-MS: 142 ( $M^+$ ).

N-*f*(tert-*Butoxy*)*carbonylJ*-N-*methyl*-D-*phenylalanine* (**3**). NaH (60% in mineral oil; 633 mg, 26.4 mmol, 14 equiv.) was added slowly in portions over a period of 2 h to a cooled (0°) soln. of N-*Boc-phenylalanine* (**25** 500 mg, 1.88 mmol) and MeI (1.1 ml, 18.8 mmol) in anh. THF (2 ml) under N<sub>2</sub>. The mixture was stirred at r.t. for 24 h under N<sub>2</sub> and then diluted with Et<sub>2</sub>O (20 ml), and the reaction was quenched with H<sub>2</sub>O (30 ml). The layers were separated, and the aq. layer was extracted with Et<sub>2</sub>O (2 × 15 ml), acidified to pH 3 with a 20% aq. soln. of citric acid, and extracted with AcOEt (3 × 20 ml). The combined org. phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to afford **3** (515 mg, 98%). Thick colorless oil. [ $\alpha$ ]<sub>25</sub><sup>25</sup> = +60.2 (*c* = 1, CHCl<sub>3</sub>). <sup>1</sup>H-NMR: 7.37 – 7.14 (*m*, 5 H); 4.91 – 4.81 (*m*, 0.5 H); 4.69 – 4.58 (*m*, 0.5 H); 3.40 – 3.25 (*m*, 1 H); 3.18 – 2.95 (*m*, 1 H); 2.76 (*s*, 1.5 H); 2.68 (*s*, 1.5 H); 1.39 (*s*, 4.5 H); 1.34 (*s*, 4.5 H). <sup>13</sup>C-NMR: 176.3; 156.4; 137.5; 129.1; 128.7; 126.8; 80.8; 61.5; 35.3; 32.9; 28.3. ESI-MS: 302 ([*M*+Na]<sup>+</sup>). HR-MS: 302.1364 ([*M*+Na]<sup>+</sup>, C<sub>15</sub>H<sub>21</sub>NNaO<sup>4</sup><sub>4</sub>; calc. 302.1368).

(3R,5R)-9-(Benzyloxy)-3-methylnon-1-en-7-yn-5-yl N-[(tert-Butoxy)carbonyl]-N-methyl-D-phenylalaninate (26). To a flask containing 4 (450 mg1.74 mmol) was added THF (20 ml) under Ar. Ph<sub>3</sub>P (1.58 g, 6.12 mmol), and **3** (1.7 g, 6.12 mmol) were added at r.t. The mixture was cooled to 0°, followed by dropwise addition of diisopropyl azodicarboxylate (0.96 ml, 4.87 mmol). The combined pale-yellow mixture was stirred at r.t. overnight and directly concentrated under reduced pressure. Further purification by flash CC (20% AcOEt/hexane) gave **26** (588 mg, 65%). Colorless oil.  $[a]_{D}^{25} = +2.5$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 2936, 2862, 1735, 1697, 1451, 1366, 11219, 1165, 1098, 761. <sup>1</sup>H-NMR: 7.44–7.12 (m, 10 H); 5.74–5.53 (m, 1 H); 5.07–4.78 (m, 3 H); 4.51 (s, 2 H); 4.16 (s, 2 H); 3.41–3.25 (m, 1 H); 3.06–2.85 (m, 1 H); 2.77 (s, 3 H); 2.62–2.49 (m, 2 H); 2.30–2.11 (m, 1 H); 1.83–1.58 (m, 3 H); 1.36 (s, 9 H); 1.07–0.95 (m, 3 H). <sup>13</sup>C-NMR: 170.6; 170.4; 155.0; 155.6; 142.8; 137.4; 128.8; 128.3; 127.9; 127.7; 126.5; 126.4; 114.0; 82.1; 81.7; 80.1; 78.5; 71.3; 71.1; 60.6; 59.6; 57.5; 39.9; 35.0; 34.9; 34.5; 34.4; 31.8; 31.0; 28.1; 24.6; 20.8. ESI-MS: 542 ([M + Na]<sup>+</sup>). HR-MS: 542.2886 ([M + Na]<sup>+</sup>, C<sub>32</sub>H<sub>41</sub>NNaO<sup>+</sup><sub>5</sub>; calc. 542.2882).

(3R,5R)-9-(Benzyloxy)-3-methylnon-1-en-7-yn-5-yl N-Methyl-D-phenylalaninate (**27**). To a soln. of **26** (400 mg, 0.77 mmol) in 3 ml of dry CH<sub>2</sub>Cl<sub>2</sub> under Ar was added CF<sub>3</sub>CO<sub>2</sub>H (0.61 ml, 7.7 mmol) at 0°. After stirring for 3 h at 23°, the reaction was quenched with sat. aq. NaHCO<sub>3</sub>, and the mixture was extracted with AcOEt, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Purification by CC (SiO<sub>2</sub>; hexane/AcOEt 60:40) gave **27** (289 mg, 90%). Colorless oil.  $[a]_D^{25} = -21.5$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3030, 2924, 2854, 2232, 1736, 1642, 1453, 1260, 1195, 1073, 1026, 772. <sup>1</sup>H-NMR: 7.44–7.12 (m, 10 H); 5.61–5.47 (m, 1 H); 4.93–4.78 (m, 3 H); 4.51 (s, 2 H); 4.01 (s, 2 H); 3.41 (t, J = 6.8, 1 H); 2.89 (d, J = 6.8, 2 H); 2.53–2.39 (m, 2 H); 2.32 (s, 3 H); 1.93–1.85 (m, 1 H); 1.61–1.43 (m, 2 H); 0.89 (d, J = 6.8, 3 H). <sup>13</sup>C-NMR: 173.4; 142.4; 136.7; 128.7; 128.0; 127.5; 127.3; 126.2; 113.5; 81.7; 77.9; 70.9; 70.4; 64.2; 57.1; 39.6; 39.0; 34.2; 33.6; 24.3; 20.4. ESI-MS: 420 ( $[M + H]^+$ ). HR-MS: 420.2545 ( $[M + H]^+$ , C<sub>27</sub>H<sub>34</sub>NO<sub>3</sub><sup>+</sup>; calc. 420.2539).

(3R,5R)-9-(*Benzyloxy*)-3-methylnon-1-en-7-yn-5-yl N-[(2S,4R)-2,4-Dimethylhex-5-enoyl]-N-methylp-phenylalaninate (**28**). DIPEA (0.16 ml, 0.94 mmol) was added to a soln. of **27** (200 mg, 0.47 mmol) and **5** (81.2 mg, 0.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at 0°. PyBOP (297 mg, 0.57 mmol) was added at 0°, and the resulting mixture was stirred for 10 h at r.t., and the reaction was quenched with sat. aq. NH<sub>4</sub>Cl, and the mixture was extracted with AcOEt, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Purification by CC (SiO<sub>2</sub>; hexane/AcOEt 20:80) gave **28** (181 mg, 70%). Colorless oil.  $[a]_{15}^{25} = +30.4$  (c = 1, CHCl<sub>3</sub>). IR (KBr): 3066, 2961, 2924, 2239, 1951, 1737, 1647, 1455, 1261, 1090, 1022, 800, 699. <sup>1</sup>H-NMR: 7.43 – 7.11 (m, 10 H); 5.71 – 5.35 (m, 2 H); 5.08 – 4.77 (m, 5 H); 4.57 (s, 2 H); 4.15 (s, 2 H); 3.47 – 3.27 (m 1 H); 3.05 – 2.87 (m, 2 H); 2.81 (s, 3 H); 2.59 – 2.48 (m, 2 H); 2.27 – 2.07 (m, 3 H); 1.88 – 1.50 (m, 4 H); 1.06 – 0.87 (m, 6 H); 0.69 (d, J = 6.8, 2.4 H); 0.58 (d, J = 6.8, 0.6 H). <sup>13</sup>C-NMR: 1770; 170.9; 144.0; 143.1; 137.5; 1370; 129.8; 128.3; 128.4; 127.9; 126.6; 113.2; 112.8; 82.1; 79.1; 72.9; 71.2; 65.0; 57.5; 40.0; 36.9; 34.7; 34.4; 33.2; 32.2; 24.6; 20.8; 20.1. ESI-MS: 544 ([M + H]<sup>+</sup>). HR-MS: 544.3432 ([M + H]<sup>+</sup>, C<sub>35</sub>H<sub>46</sub>NO<sup>+</sup><sub>4</sub>; calc. 544.3427).

Cobalt Complex (**31**). To a soln. of **28** (30 mg, 0.05 mmol) in toluene (5 ml) was added  $[Co_2(CO)_8]$  (26.4 mg, 0.77 mmol). The mixture was stirred at r.t. for 30 min, and the solvent was removed under reduced pressure. The dark residue was purified by flash CC (5% AcOEt in hexane) to give **31** (46 mg, 98%) as a red oil, an inseparable mixture of diastereoisomers, which was used immediately in the next step.

(3R,6S,8R,11R,13R)-3-Benzyl-13-[4-(benzyloxy)but-2-yn-1-yl]-4,6,8,11-tetramethyl-1-oxa-4-azacyclotridec-9-ene-2,5-dione (**32**). To a soln. of **31** (20 mg, 0.024 mmol) in dry toluene (120 ml) was added second-generation *Grubbs* catalyst (6.1 mg, 0.0072 mmol). The resulting soln. was heated to 110° for 10 h, then cooled to r.t. and filtered through a plug of SiO<sub>2</sub>. The solvent was removed under reduced pressure. The residue was purified by flash CC (20% AcOEt/hexane) to give **32** (3.5 mg, 30%). Brown oil.  $[a]_{25}^{25} = +70.0 (c = 1, CHCl_3)$ . IR (KBr): 2959, 2923, 2234, 1737, 1705, 1649, 1454, 1405, 1374, 1260, 1219, 1087, 1019, 772. <sup>1</sup>H-NMR: 7.43 – 7.13 (m, 10 H); 5.02 – 4.72 (m, 3 H); 4.54 (s, 2 H); 4.18 (s, 2 H); 3.49 – 3.31 (m, 1 H); 3.11 – 2.97 (m, 1 H); 2.81 (s, 3 H); 2.66 – 2.51 (m, 1 H); 2.28 – 1.97 (m, 5 H); 1.72 – 1.42 (m, 4 H); 1.32 – 1.27 (m, 4 H); 1.06 (d, J = 6.6, 3 H); 0.80 (d, J = 6.7, 2 H). <sup>13</sup>C-NMR: 176.4; 170.1; 138.0; 136.3; 135.5; 133.2; 129.0; 128.3; 128.2; 127.8; 125.6; 83.2; 81.5; 73.0; 72.0; 60.7; 46.5; 40.0; 39.7; 38.9; 36.8; 34.8; 33.8; 29.8; 20.5; 19.8; 19.3; 18.5. ESI-MS: 516 ([M + H]<sup>+</sup>). HR-MS: 516.3119 ([M + H]<sup>+</sup>, C<sub>33</sub>H<sub>42</sub>NO<sub>4</sub><sup>+</sup>; calc. 516.3114). The authors gratefully acknowledge keen interest shown by Dr. J. S. Yadav, Director, IICT, Hyderabad. G. V. R. thanks UGC, New Delhi, for financial support.

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