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Synthesis of Spinosyn Analogues for Modern Crop Protection

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Dedicated to Professor Theophil Eicher on the occasion of his 80th birthday

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New spinosyn analogues **3** with an arene group as ring A and containing a L-rhamnose moiety have been prepared. The key step in the synthesis of **3** is a Pd-catalyzed twofold Heck reaction of glycosylated bromoarene **4**, containing an iodovinyl side chain and a tri-*O*-methyl-L-rhamnose moiety with the cyclopentene-annulated macrolactone **5**. Compounds **3** may be of interest as new insecticides.

Introduction

Spinosyns represent a family of natural products produced by the soil organisms *Saccharopolyspora spinosa*[1] and *Saccharopolyspora pogona*[2] with a strong insecticidal activity.[3] They are used for crop protection and have been commercialized since 1997 as Spinosad, an 85:15 mixture of spinosyn A (**1a**) and D (**1b**), which is produced by fermentation using *Saccharopolyspora spinosa* (Figure 1). The spinosyns have a tetracyclic backbone, which contains a 12-membered macrocyclic lactone and two sugar moieties. Spinosyn D (**1b**) differs from spinosyn A (**1a**) by an additional methyl group at the B-ring. A recent highly successful development is the generation of semisynthetic spinetoram (**2**) containing 3′-*O*-ethyl-5,6-dihydrospinosyn J as the major component (Figure 1).[4]

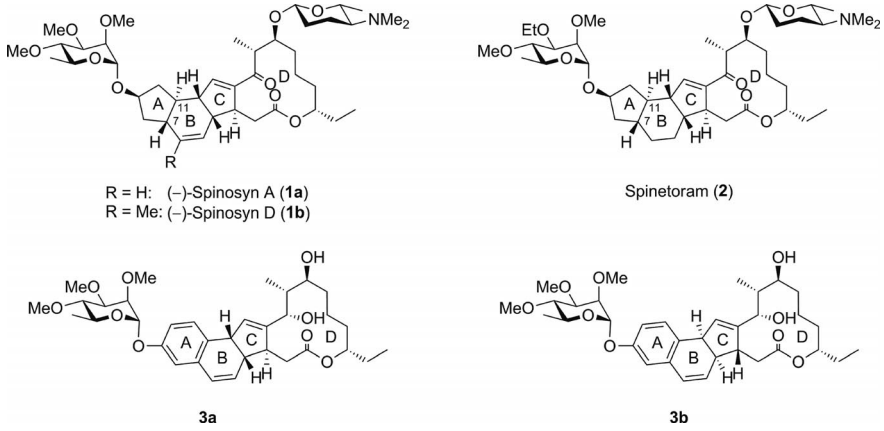

Figure 1. Naturally occurring spinosyns **1**, spinetoram **2** and spinosyn analogues **3a** and **3b**.

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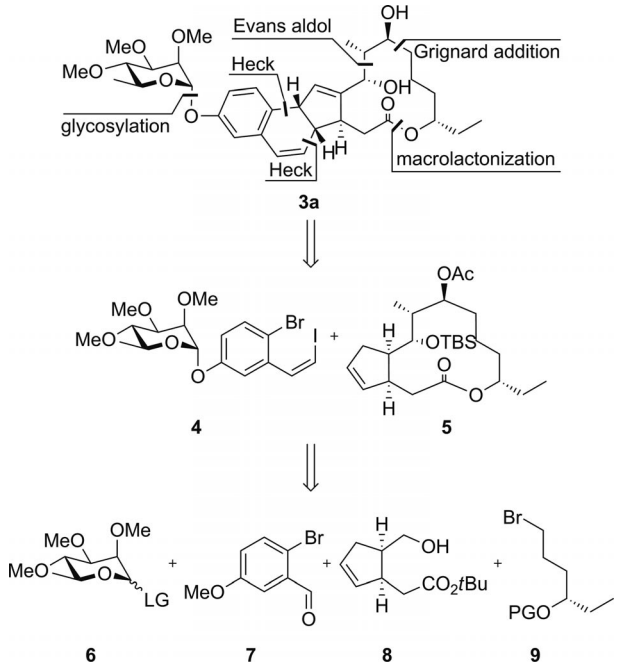
The mode of action of these insecticides is unique though not fully understood. The compounds kill target insects due to exhaustion of the firing capability of the neurons. So far they seem to target the nicotinic acetylcholine receptor (nAChR) subunit Dα6[5] and to interact with the γ-amino butyric acid (GABA) receptor. Spinosad is highly selective relative to other insecticides and thus, is non-toxic to mammals and has little to no effect on non-target insects and

fish.[3c,6] This selectivity, combined with an excellent environmental profile, makes spinosad an important crop protecting agent.

Due to the recent development of resistance to the spinosyns by target insects new spinosyn analogues are highly desirable.[7] Although little is known about structure–activity relationships (SAR) for the spinosyns, the existing data show that an additional double bond between C-7 and C-11 has no negative effects on the biological activity. Instead, a slight increase in the insecticidal activity has been noted with the addition of this functionality.[8] Based on this finding we have designed new spinosyn analogues with reduced complexity. Our work is focused on the synthesis of compounds containing a double bond between C-7 and C-11 as part of an aromatic ring A instead of the cyclopentane moiety observed with the natural spinosyns. In this way we can circumvent the issue of introducing and controlling three stereogenic centers. We have recently reported on a convergent synthesis of a spinosyn analogue devoid of any sugar moieties.[9] Here we describe the synthesis of analogues **3** containing a tri-*O*-methyl-L-rhamnose moiety using a twofold Heck reaction and glycosylated bromoarene **4** containing an iodovinyl side chain and cyclopentene-annulated macrolactone **5** (Scheme 1). This route is highly flexible and allows the synthesis of analogues with different constitutions and stereochemistry, which are envisioned to be useful in carrying out SAR studies.

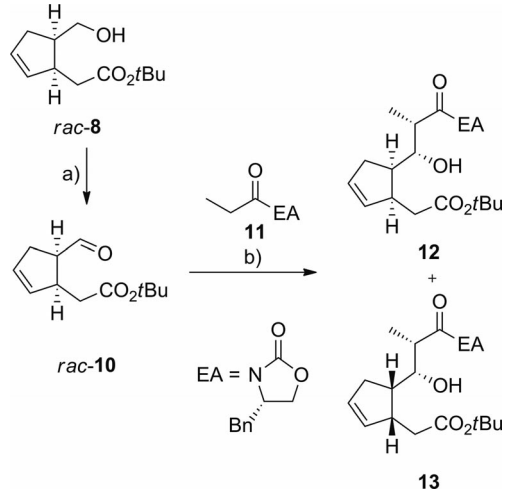


Scheme 1. Retrosynthesis of spinosyn analogue **3a**.

Results and Discussion

The retrosynthetic analysis of spinosyn analogue **3a** suggests the application of two Heck reactions involving **4** and **5**. Aryl bromide **4** could be envisioned to arise from tri-*O*-methyl-L-rhamnose **6**, and bromobenzaldehyde **7** whereas macrolactone **5** could be generated from 1,2-*cis*-disubstituted cyclopentene **8** and hexane derivative **9** (Scheme 1). The *cis*-orientation of the two substituents in **8**, and finally in the macrolactone **5**, is necessary to allow facially selective addition *anti* to the substituents in the first Heck reaction and a Pd-H-*syn* elimination in the second Heck reaction. We have used **8** as a racemic mixture in this approach to allow the preparation of diastereomers, although it can also be employed as an enantiopure compound.[10]

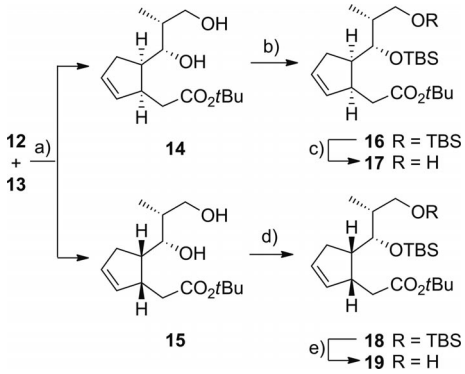
The alcohol moiety in *rac*-**8** was oxidized with Dess–Martin periodinane (DMP) in CH_2Cl_2 in 92% yield. Resulting aldehyde *rac*-**10** was then used in an Evans aldol reaction[11] with the boron-enolate of oxazolidinone **11** using NEt_3 as base. The reaction was highly stereoselective and furnished expected enantiopure diastereomers **12** and **13** as an almost 1:1 mixture; these products could not be separated by chromatography at this stage (Scheme 2). Employing the same route to enantiopure cyclopentene **8**, stereoisomer **12** was formed in the Evans aldol reaction in 83% yield.



Scheme 2. Synthesis of **12** and **13**: a) 1.50 equiv. DMP, room temp., 30 min, CH_2Cl_2, 92%; b) 1.20 equiv. **11**, 1.30 equiv. nBu_2BOTf (1 M in CH_2Cl_2), 1.50 equiv. NEt_3, 0 °C, 1 h, then addition of *rac*-**10** at –78 °C, maintain temperature for 1 h, then warm to 0 °C over course of 4 h, 92%.

Subsequent reductive removal of the Evans auxiliary in **12/13** with $LiBH_4$ and EtOH led directly to diastereomeric diols **14** and **15** as an almost 1:1-mixture. Unlike **12/13**, diols **14** and **15** could now easily be separated by column chromatography on silica gel (Scheme 3). Both hydroxy groups in **14** and **15** were then protected as TBS ethers using TBSOTf and 1,6-lutidine in CH_2Cl_2 to give **16** and **18**. Selective removal of the primary TBS group with HF/pyridine in THF/pyridine afforded enantiopure primary alcohols **17** and **19** in 97% and 90% yield, respectively (Scheme 3).

For confirmation of the proposed structure of these compounds, enantiopure **12** was treated with TBSOTf and imidazole at 60 °C to give corresponding TBS ether **20** in 82% yield, for which crystals could be obtained allowing for



Scheme 3. Synthesis of alcohols **17** and **19** a) 1.10 equiv. EtOH, 1.10 equiv. $LiBH_4$, Et_2O, –20 °C, 90 min, 45% (**14**) and 49% (**15**); b) 8.0 equiv. 2,6-lutidine, 4.0 equiv. TBSOTf, CH_2Cl_2, –10 °C, 40 min, 95% (**16**); c) HF·pyr, pyr/THF, 1:2, 0 °C→room temp., 8 h, 94% (**17**); d) 6.0 equiv. 2,6-lutidine, 3.0 equiv. TBSOTf, CH_2Cl_2, –10 °C, 45 min, 97% (**18**); e) HF·pyr, pyr/THF, 1:2, 0 °C→room temp., 14 h, 90% (**19**).

crystal structure determination (Figure 2). In this way the absolute configuration of all stereogenic centers of **20** as well as those of **17** and **19** could be unambiguously assigned.

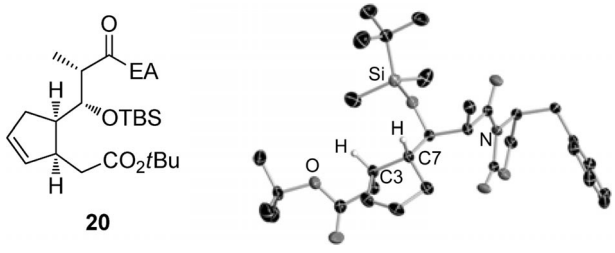
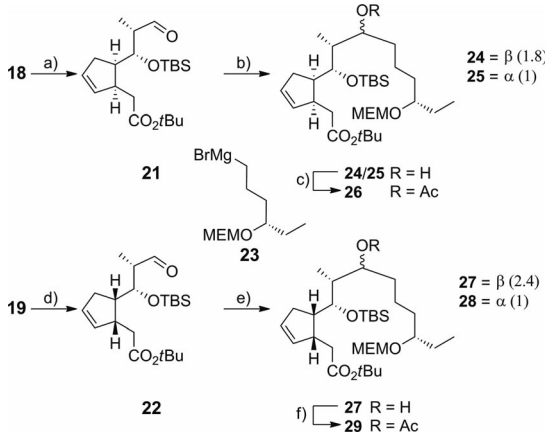


Figure 2. Structure of **20** determined by crystallography. Anisotropic displacement parameters are depicted at the 50% probability level. All hydrogen atoms except 3-H and 7-H, to illustrate the configuration at C-3 and C-7, respectively, are omitted for clarity. The disorder of the *t*Bu group is also omitted for clarity (see Supporting Information).

Alcohols **17** and **19** were oxidized with DMP in CH_2Cl_2 to give aldehydes **21** and **22**, respectively which were independently used in a Grignard reactions with enantiopure **23**. Grignard reactions were carried out in THF with and without LiCl[12] as additive. The reaction of **21** at –78 °C in the presence of LiCl led to a 1.8:1 mixture of **24** and **25** in favor of the desired (3′′*S*)-diastereomer **24**. Alcohols **24** and **25** could not be separated by chromatography at this stage; each product also contained small amounts of the Wurtz-coupled byproduct. Without the addition of LiCl the reaction was much slower and the reaction temperature had to be raised to –60 °C leading to large amounts of the Wurtz product. Unexpectedly, the ratio of the diastereomers thus generated was almost the same as was the case at –78 °C with a 24/25 ratio of 1.6:1. The Grignard reaction of aldehyde **22** with **23** in the presence of LiCl at –78 °C yielded two diastereomers **27** and **28** in a 2.4:1 ratio in favor of **27**, which could be separated from **28** by column chromatography on silica gel. Removal of small amounts of the corresponding Wurtz product formed in the reaction was possible by RP chromatography.

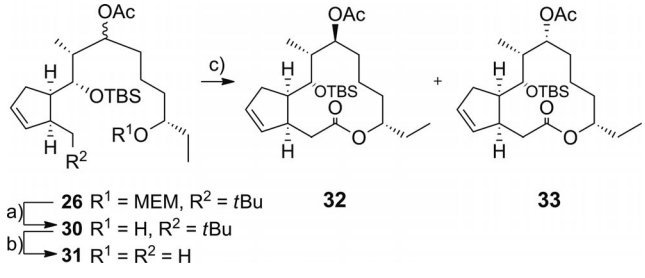
The preferred formation of diastereomers **24** and **27** can be explained by applying the Felkin–Anh model.[13]

Acetylation of the mixture of **24** and **25** using an excess of Ac_2O and NEt_3 and catalytic amounts of DMAP in CH_2Cl_2 afforded diastereomeric mixture **26** in 83% yield based on aldehyde **21**. As described for **24/25**, the same transformation was applied to alcohol **27** to give acetate **29** in 66% based on aldehyde **22** (Scheme 4).



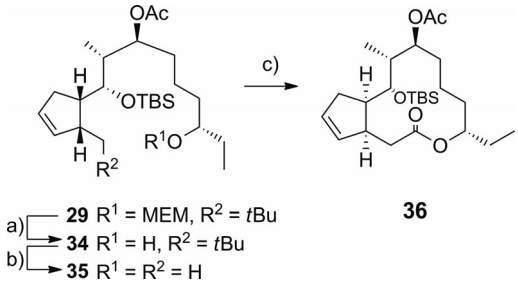
Scheme 4. a) 3.0 equiv. DMP, CH_2Cl_2, 4 h, quant.; b) 1.30 equiv. **23**, THF, LiCl, –78 °C; c) 8.0 equiv. NEt_3, 5.0 equiv. Ac_2O, 20.0 mol-% DMAP, CH_2Cl_2, room temp., 4 h, 83% (based on **21**); d) 3.0 equiv. DMP, CH_2Cl_2, 4 h, 83%; e) 1.30 equiv. **23**, THF, LiCl, –78 °C; f) 8.0 equiv. NEt_3, 5.0 equiv. Ac_2O, 20.0 mol-% DMAP, CH_2Cl_2, room temp., 4 h, 66% (based on **22**).

Cleavage of the MEM ether in **26** with TMSI,[14] generated in situ, afforded compounds **30** in 64% (86% brsm) and cleavage of the *tert*-butyl ester with TMSOTf and 2,6-lutidine in THF led to acids **31** in 95% yield. Macrolactonization following Yamaguchi's procedure[15] using 2,4,6-trichlorobenzoyl chloride (TCBzCl) gave a mixture of macrolactones **32** and **33** in 45% and 12% yield, respectively, which could be separated by column chromatography on silica gel (Scheme 5).

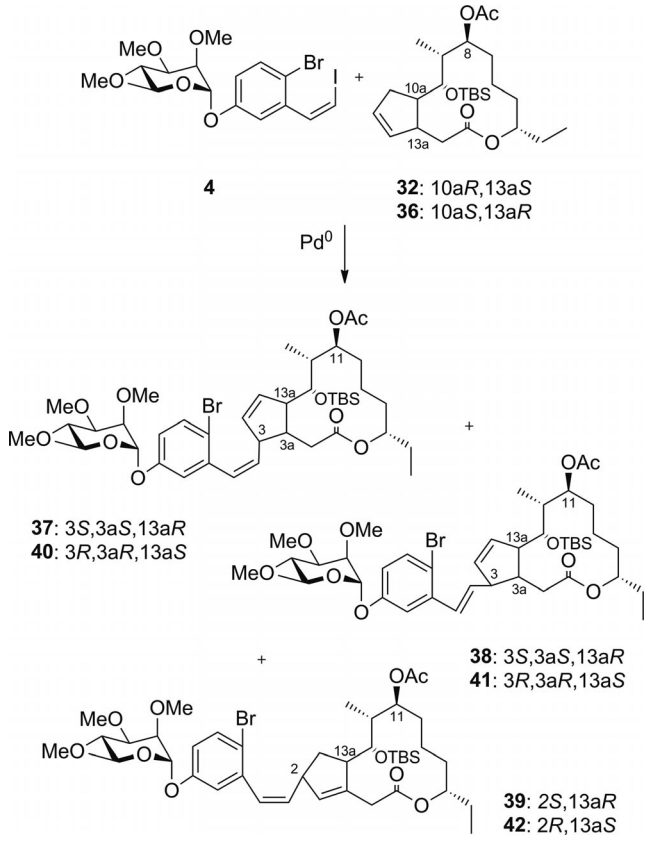


Scheme 5. a) 2.2 equiv. TMSCl, 2.20 equiv. NaI (in three portions), CH_3CN/CH_2Cl_2 (4:1), –45 °C, 4 h, 64% (86% brsm); b) 14.0 equiv. 2,6-lutidine, 7.0 equiv. TMSOTf, THF, room temp., 1.5 h, 95%; c) 6.0 equiv. NEt_3, 4.0 equiv. TCBzCl, THF, room temp., 1.5 h, then slow addition (syringe pump) to 10.0 equiv. DMAP, toluene, 60 °C, 165 min, 45% (**32**) and 12% (**33**).

The MEM ether cleavage of acetate **27** with in TMSI, generated in situ, led to secondary alcohol **34** in 65% yield. Hydrolysis of the *tert*-butyl ester with TMSOTf and 2,6-lutidine in THF furnished acid **35** in 96% yield and subsequent macrolactonization afforded macrolactone **36** in 96% yield (Scheme 6).

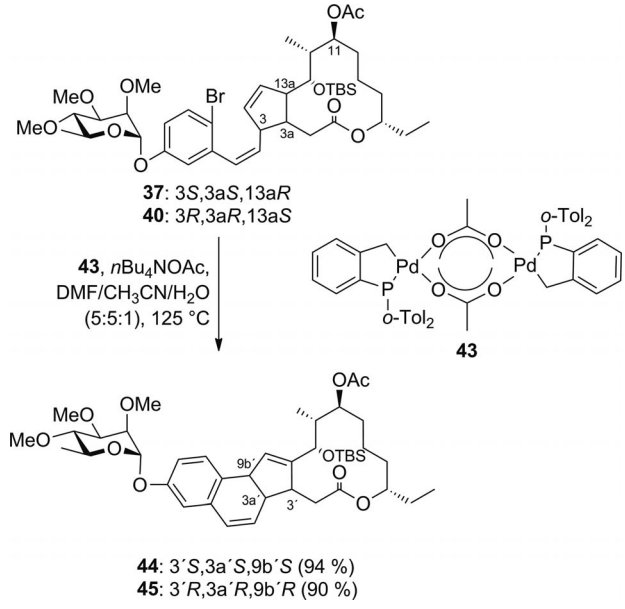


Scheme 6. a) 2.40 equiv. TMSCl, 2.40 equiv. NaI (in three portions), CH_3CN/CH_2Cl_2 (3.5:1), –45 °C, 5 h, 65% (84% brsm); b) 14.0 equiv. 2,6-lutidine, 7.0 equiv. TMSOTf, THF, room temp., 4.3 h, 96%; c) 6.0 equiv. NEt_3, 4.0 equiv. TCBzCl, THF, room temp., 1.5 h, then slow addition (syringe pump) to 10.0 equiv. DMAP, toluene, 60 °C, 165 min, 96%.



Scheme 7. Intermolecular Heck reaction.

Macrolactones **32** and **36** were subsequently used in the twofold Heck reaction. For the first, intermolecular, step $Pd(OAc)_2$, TBACl[16] (Scheme 7) and an inorganic base in DMF were employed. The second, intramolecular, Heck coupling exploited Herrmann–Beller catalyst **43** and the base *n*-Bu_4NOAc in $DMF/CH_3CN/H_2O$ (5:5:1) (Scheme 8).[17]



Scheme 8. Intramolecular Heck reaction of **37** and **40** respectively.

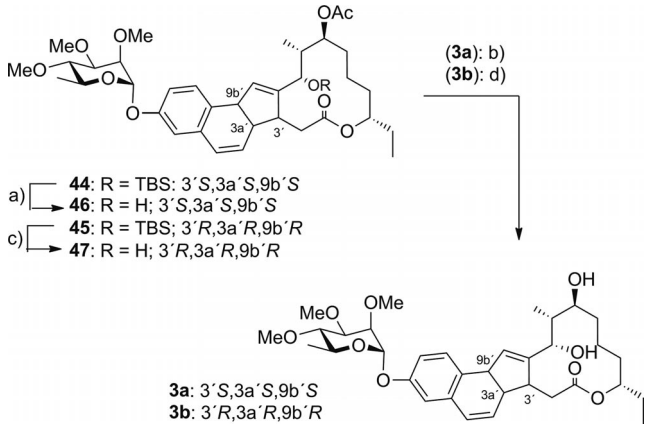
Initial Heck reaction of **32** and **36** gave desired products **37** and **40** in 26% and 33% yield, respectively (Table 1). In addition, regioisomers **39** and **42** as well as *E*-isomers **38** and **41** were obtained. The corresponding *E*-isomers of **39** and **42** were not found. The overall yields for these transformations were very high nearing 100% (Scheme 7). One drawback to this approach however, was that considerable amounts of the *E*-isomers were formed, which cannot be used in the second Heck reaction.

The second Heck reaction using Z-isomers **37** and **40**, respectively led to desired tetracyclic products **44** and **45** in over 90% yield. Subsequent cleavage of the TBS ether with HF·pyr at 60 °C followed by removal of the acetyl-protecting group with K_2CO_3 in MeOH at 0 °C yielded spinosyn analogues **3a** and **3b** in high yields (Scheme 9).

Table 1. Summary of Intermolecular Heck reaction results.[a]

Entry	SM	Catalyst loading	Base	Reaction temp.	Time (d)	Products and yields (%)		
1	**32**	10 mol-%	NaOAc[b]	room temp.	2	**37** (20)	**38** (45)	**39** (11)
2	**32**	3 mol-%	NaOAc	0 °C	7	**37** (26)	**38** (63)	**39** (11)
3	**32**	3 mol-%	Na_2CO_3	room temp.	2	**37** (9)	**38** (54)	**39** (20)
4	**36**	3 mol-%	NaOAc	0 °C	8	**40** (33)	**41** (58)	**42** (<5)

[a] Conditions: Starting material: **31** and **36**, respectively; base (1.0 equiv.), $Pd(OAc)_2$, TBACl (0.3 equiv.), DMF. [b] 0.7 equiv.



Scheme 9. Synthesis of **3a** and **3b**: a) HF·pyr, pyr/THF, 1:3, 60 °C, 16 h, 96%; b) 1.0 equiv. K_2CO_3, MeOH, 0 °C (2.5 h)→room temp. (4 h), 66% (82% brsm); c) HF·pyr, pyr/THF, 1:3, 60 °C, 15.5 h, 96%; d) 1.0 equiv. K_2CO_3, MeOH, 0 °C (80 min)→room temp. (4 h), 81% (89% brsm).

Conclusions

We have reported on the synthesis of spinosyn A analogues **3a** and **3b** containing a tri-*O*-methyl-L-rhamnose moiety using a twofold Heck reaction sequence to construct the tetracyclic backbone. Further reactions employed to generate **3a** and **3b** include a stereoselective Evans-aldol reaction, a Grignard addition and Yamaguchi macrolactonization. The aim of this work is to prepare new spinosyns that enable improved pest management by circumventing mechanisms of spinosyn resistance.

Experimental Section

General Methods: All reactions were performed under argon atmosphere. THF and diethyl ether were dried and distilled prior usage by usual laboratory methods. All other solvents were used from commercial sources and stored over molecular sieves. All reagents were obtained from commercial sources and were used without further purification. Thin-layer-chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates (Merck) and silica gel 60 (0.063–0.200 mm, *Merck*) was used for column chromatography. Phosphomolybdic acid in methanol or vanillin in methanolic sulfuric acid were used as staining reagents. UV spectra were taken in CH_3CN or MeOH with a Perkin–Elmer Lambda 2 spectrometer or a JASCO V-630. IR spectra were recorded as KBr pellets or as film between NaCl plates with a Bruker IFS 25 spectrometer or neat (ATR) with a JASCO FT/IR-4100. ^{1}H- and ^{13}C-spectra were recorded with UNITY 300 (300 MHz), MERCURY-Vx (300 MHz), VNMRS-300 (300 MHz) and INOVA-600 (600 MHz) Varian spectrometers. Chemical shifts are reported in ppm with the solvent as internal standard.

The following abbreviations are used: MTBE (methyl *tert*-butyl ether), PE (petroleum ether b.p. 40–60 °C), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad) and combinations thereof.

Single-crystal structural analysis: Single crystals were selected from a flask that was stored at –18 °C for two weeks and covered with perfluorated polyether oil on a microscope slide, which was cooled with a nitrogen gas flow using the XTEMP2 to avoid melting of the crystals.[18] An appropriate crystal was selected using a polarized microscope, mounted on the tip of a MITEGEN©MicroMount, fixed to a goniometer head and shock-cooled by the crystal cooling device.

The data for **20** were collected from a shock-cooled crystal at 100(2) K on a BRUKER TXS-Mo rotating anode (used Mo-K_α radiation, λ = 71.073 pm) with mirror optics and APEX II detector with a D8 goniometer. The data of **20** were integrated with SAINT[19] and an empirical absorption correction (SADABS)[20] was applied. The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares methods against F^2 (SHELXL-97)[21] implemented in the SHEXLE GUI.[22] All non-hydrogen-atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to equal to 1.5 times the U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Disordered moieties were refined using geometric and anisotropic displacement parameter restraints.

The CCDC number, crystal data and experimental details for the X-ray measurements are also listed in the Supporting Information CCDC-879948 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.

Compound 37: A solution of the vinylic iodide **4** (64.5 mg, 126 µmol, 1.0 equiv.) and cyclopentene derivative **32** (171 mg, 377 µmol, 3.0 equiv.) in abs. DMF (3 mL) was degassed and $Pd(OAc)_2$ (847 µg, 3.77 µmol, 3 mol-%), NaOAc (31.3 mg, 377 µmol, 3.0 equiv.) and TBACl (34.9 mg, 126 µmol, 1.0 equiv.) were added at room temp., the reaction mixture was cooled to 0 °C and stirred under exclusion of light at 0 °C for 7 d. The mixture was then diluted with Et_2O (30 mL) and water (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layer were washed with brine (20 mL), dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/Et_2O, 2:1→PE/AcOEt, 1:1) gave the pure product **37** (27.5 mg, 32.8 µmol, 26%) as a light brown oil. In addition, a mixture of **37** and **39** [11.9 mg, 14.2 µmol, 11%, ca. 2:1 (**37**/**39**)] as well as **38** (66.0 mg, 78.8 µmol, 63%) were obtained.

Analytical Data of 37: R_f = 0.32 (PE/AcOEt, 3:1). $[\alpha]_D^{20}$ = –108.0 (*c* = 0.7 , in $CHCl_3$). UV (MeCN): λ_{max} (lg ε) = 198.5 (4.398), 215.0 (4.365), 286.0 (3.100) nm. IR (film): $\tilde{\nu}$ = 2932, 1729, 1566, 1463, 1373, 1247, 1198, 1104, 1049, 1009, 902, 866, 837, 807, 774, 732, 703, 664 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.15, –0.09 (2 × s, 2 × 3 H, $SiCH_3$), 0.62 [s, 9 H, $SiC(CH_3)_3$], 0.81–0.89 (m, 6 H, 7-CH_2CH_3, 12-CH_3), 1.24 (d, *J* = 9.6 Hz, 3 H, 6′′′-H_3), 1.04–1.13 (m, 1 H), 1.17–1.31 (m, 1 H), 1.43–1.70 (m, 5 H), 1.73–1.82 (m, 2 H) (8-H_2, 9-H_2, 10-H_2, 12-H, 7-CH_2CH_3), 1.99 [s, 3 H, OC(O)CH_3], 2.37 (m_c, 1 H, 3a-H), 2.48 (d, *J* = 18.0 Hz, 1 H, 4-H_A), 2.94 (dd, *J* = 18.6, 12.6 Hz, 1 H, 4-H_B), 3.16 (t, *J* = 9.6 Hz, 1 H, 4′′′-H), 3.20 (m_c, 1 H, 3-H), 3.29 (m_c, 1 H, 13a-H), 3.35 (d, *J* = 10.8 Hz, 1 H, 13-H), 3.51, 3.52, 3.53 (3 × s, 3 × 3 H, 3 × OCH_3), 3.55–3.60 (m, 1 H, 5′′′-H), 3.63 (dd, *J* = 9.0, 3.0 Hz, 1 H, 3′′′-H), 3.68 (m_c, 1 H, 2′′′-H), 4.95 (m_c, 1 H, 7-H), 5.29 (m_c, 1 H, 11-H), 5.40 (t, *J* = 10.8 Hz, 1 H, 1′-H), 5.45 (d, *J* = 1.2 Hz, 1 H, 1′′′-H), 5.53–5.57 (m, 1 H), 5.65–5.68 (m, 1 H) (1-H, 2-H), 6.43 (d, *J* = 10.8 Hz, 1 H, 2′-H), 6.79 (d, *J* = 3.0 Hz, 1 H, 6′′-H), 6.86 (dd, *J* = 9.0 Hz, 2.4 Hz, 1 H, 4′′-H), 7.41 (d, *J* = 8.4 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = –4.5, –1.3 (2 × $SiCH_3$), 9.6, 10.0 (C-7-CH_2CH_3, C-12-CH_3), 17.8 (C-6′′′), 18.0 [$SiC(CH_3)_3$], 21.1 [OC(O)-

CH_3], 19.8, 28.0, 30.6, 30.8 (C-8, C-9, C-10, C-7-CH_2CH_3), 26.3 [SiC(CH_3)$_3$], 34.2 (C-4), 38.3 (C-12), 44.1 (C-3a), 47.2 (C-13a), 50.7 (C-3), 57.8, 59.2, 60.9 (3×OCH_3), 68.6 (C-5′′′), 71.9 (C-11), 76.2 (C-7), 77.1 (C-2′′′), 77.3 (C-13), 80.7 (C-3′′′), 81.8 (C-4′′′), 95.0 (C-1′′′), 115.3 (C-4′′), 116.0 (C-2′′), 119.3 (C-6′′), 130.6 (C-2′), 133.1 (C-3′′), 134.5, 135.8 (C-1, C-2), 136.7 (C-1′), 138.9 (C-1′′), 155.2 (C-5′′), 170.7, 173.2 [C-5, OC(O)CH_3] ppm. MS (DCI): *m/z* (%) = 856.5 (100) [M + NH_4]$^+$. HRMS (ESI) *m/z*: calcd. for $C_{42}H_{65}BrO_{10}Si$: 854.38686 [M + NH_4]$^+$, found 854.38665 [M + NH_4]$^+$.

Compound 44: A solution of **37** (63.8 mg, 76.1 μmol, 1.0 equiv.) and nBu$_4$NOAc (45.9 mg, 152.3 μmol, 2.0 equiv.) in DMF/CH_3CN/H_2O (5 mL, 5:5:1) was degassed and Pd-catalyst **43** (5.0 mg, 5.33 μmol, 7.0 mol-%) was added at room temp. The mixture was stirred for 5 min at room temp. and warmed to 125 °C for 1.75 h. The mixture was cooled to room temp., diluted with Et_2O (15 mL) and washed with water (15 mL). The aqueous layer was extracted with Et_2O (2×15 mL), the combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 5:1) gave the tetracycle **44** (54.0 mg, 71.3 μmol, 94%) as a colourless oil.

R_f = 0.27 (PE/AcOEt, 3:1). $[\alpha]_D^{20}$ = –169.6 (c = 1.14 , in $CHCl_3$). UV (MeCN): λ_{max} (lgε) = 227.0 (4.431), 265.0 (3.768), 275.0 (3.695), 299.0 (3.247) nm. IR (film): $\tilde{\nu}$ = 2930, 1732, 1603, 1573, 1498, 1463, 1376, 1249, 1103, 1020, 871, 836, 775, 737, 704, 665 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = –4.78, –4.25 (2×s, 2×3 H, 2×SiCH_3), 0.79 (d, J = 6.6 Hz, 3 H, 2′′-CH_3), 0.81 [s, 9 H, SiC(CH_3)$_3$], 0.81 (t, J = 7.2 Hz, 3 H, 9′′-H$_3$), 1.23 (d, J = 6.0 Hz, 3 H, 6′′′-H$_3$), 1.20–1.32 (m, 2 H), 1.46–1.66 (m, 4 H), 1.70–1.77 (m, 1 H), 1.93–2.00 (m, 1 H) (4′′-H$_2$, 5′′-H$_2$, 6′′-H$_2$, 8′′-H$_2$), 1.82 (m$_c$, 1 H, 2′′-H), 1.97 [s, 3 H, OC(O)CH_3], 2.63 (dd, J = 16.2, 8.4 Hz, 1 H, 2-H$_A$), 2.69 (dd, J = 16.2, 2.4 Hz, 1 H, 2-H$_B$), 3.03–3.09 (m, 1 H, 3a′-H), 3.16 (t, J = 9.6 Hz, 1 H, 4′′′-H), 3.19–3.25 (m, 1 H, 3′-H), 3.52, 3.53, 3.54 (3×s, 3×3 H, 3×OCH_3), 3.61–3.66 (m, 2 H, 3′′′-H, 5′′′-H), 3.71 (dd, J = 3.0, 1.8 Hz, 1 H, 2′′′-H), 4.02 (d, J = 9.0 Hz, 1 H, 9b′-H), 4.28 (d, J = 3.0 Hz, 1 H, 1′′-H), 4.75 (m$_c$, 1 H, 7′′-H), 5.01–5.10 (m, 1 H, 3′′-H), 5.48 (d, J = 1.8 Hz, 1 H, 1′′′-H), 5.55 (s, 1 H, 1′-H), 5.80 (dd, J = 9.6, 3.0 Hz, 1 H, 4′-H), 6.24 (dd, J = 9.6, 1.8 Hz, 1 H, 5′-H), 6.68 (d, J = 3.0 Hz, 1 H, 6′-H), 6.83 (dd, J = 8.4, 3.0 Hz, 1 H, 8′-H), 7.00 (d, J = 8.4 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.8, –4.3 (2×SiCH_3), 9.7 (C-9′′), 10.8 (C-2′′-CH_3), 17.8 (C-6′′′), 18.3 [SiC(CH_3)$_3$], 19.9 (C-5′′), 21.1 [OC(O)CH_3], 25.9 [SiC(CH_3)$_3$], 27.7, 30.4, 31.1 (C-4′′, C-6′′, C-8′′), 39.9 (C-2), 43.8 (C-9b′, C-2′′), 47.5 (C-3′), 50.1 (C-3′), 57.8, 59.2, 60.9 (3×OCH_3), 68.5 (C-5′′′), 72.9 (C-1′′), 74.8 (C-3′′), 77.3 (C-2′′′), 77.6 (C-7′′), 80.9 (C-3′′′), 82.0 (C-4′′′), 95.2 (C-1′′′), 114.7 (C-6′), 114.9 (C-8′), 126.1 (C-5′), 128.2 (C-9′*), 128.7 (C-9′), 131.1 (C-4′), 133.1 (C-5′*), 133.4 (C-1′), 146.5 (C-2′), 155.0 (C-7′), 170.4, 171.5 [C-1, OC(O)CH_3] ppm. MS (DCI): *m/z* (%) = 774.4 (100) [M + NH_4]$^+$. HRMS (ESI) *m/z*: calcd. for $C_{42}H_{64}O_{10}Si$: 779.41610 [M + Na]$^+$, found 779.41571 [M + Na]$^+$.

Compound 40: A solution of vinylic iodide **4** (190 mg, 370 μmol, 1.0 equiv.) and cyclopentene derivative **36** (502 mg, 1.10 mmol, 3.0 equiv.) in abs. DMF (10 mL) was degassed and Pd(OAc)$_2$ (2.49 mg, 11.1 μmol, 3.0 mol-%), NaOAc (91.1 mg, 1.10 mmol, 3.0 equiv.) and TBACl (103 mg, 370 μmol, 1.0 equiv.) were added at room temp., the reaction mixture was cooled to 0 °C and stirred under the exclusion of light at 0 °C for 8 d. Then the mixture was diluted with Et_2O (90 mL) and washed with water (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2×90 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 5:1→PE/AcOEt, 4:1) gave **40** (102 mg, 122 μmol, 33%) as a white foam. In addition, **36** (341 mg, 753 μmol) and **41** (179 mg, 214 μmol, 58%) were obtained.

Analytical Data of 40: R_f = 0.37 (PE/AcOEt, 3:1). $[\alpha]_D^{20}$ = +55.5 (c = 0.8 , in $CHCl_3$). UV (MeCN): λ_{max} (lgε) = 213.0 (4.360), 286.5 (3.115) nm: IR (film): $\tilde{\nu}$ = 2931, 2856, 1731, 1564, 1462, 1382, 1292, 1247, 1104, 1048, 1032, 1010, 953, 908, 871, 835, 812, 773, 737, 671 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = –0.23, –0.03 (2×s, 2×3 H, 2×SiCH_3), 0.79 [s, 9 H, SiC(CH_3)$_3$], 0.83 (t, J = 7.4 Hz, 3 H, 7-CH_2CH_3), 0.86 (d, J = 6.7 Hz, 3 H, 12-CH_3), 1.23 (d, J = 6.1 Hz, 3 H, 6′′′-H$_3$), 1.19–1.29 (m, 2 H), 1.44–1.66 (m, 5 H), 1.76 (m$_c$, 2 H) (8-H$_2$, 9-H$_2$, 10-H$_2$, 12-H, 7-CH_2CH_3), 1.97 [s, 3 H, OC(O)CH_3], 2.24 (dd, J = 16.5, 13.0 Hz, 1 H, 4-H$_A$), 2.52 (dd, J = 16.5, 3.6 Hz, 1 H, 4-H$_B$), 2.58 (m$_c$, 1 H, 3a-H), 2.94 (m$_c$, 1 H, 13a-H), 3.15 (t, J = 9.5 Hz, 1 H, 4′′′-H), 3.23 (m$_c$, 1 H, 3-H), 3.49–3.57 (m, 1 H, 5′′′-H), 3.51, 3.52, 3.53 (3×s, 3×3 H, 3×OCH_3), 3.60 (dd, J = 9.5, 3.2 Hz, 1 H, 3′′′-H), 3.68 (dd, J = 3.2, 1.4 Hz, 1 H, 2′′′-H), 3.84 (d, J = 1.9 Hz, 1 H, 13-H), 4.72 (dd, J = 11.2, 5.0 Hz, 1 H, 7-H), 4.95–5.06 (m, 1 H, 11-H), 5.43 (d, J = 1.4 Hz, 1 H, 1′′′-H), 5.51 (t, J = 10.8 Hz, 1 H, 1′-H), 5.59 (d, J = 5.8 Hz, 1 H), 5.80 (m$_c$, 1 H) (1-H, 2-H), 6.45 (d, J = 11.2 Hz, 1 H, 2′-H), 6.84 (d, J = 3.0 Hz, 1 H, 6′′-H), 6.87 (dd, J = 8.9 Hz, 3.0 Hz, 1 H, 4′′-H), 7.44 (d, J = 8.9 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –3.2, –3.1 (2×SiCH_3), 9.2 (C-12-CH_3), 10.0 (C-7-CH_2CH_3), 17.9 (C-6′′′), 18.5 [SiC(CH_3)$_3$], 18.7 (C-9), 21.1 [OC(O)-CH_3], 26.2 [SiC(CH_3)$_3$], 28.6, 31.1, 32.0 (C-8, C-10, C-7-CH_2CH_3), 34.2 (C-4), 43.4 (C-12), 45.4 (C-3a), 49.6 (C-3), 53.0 (C-13a), 58.1, 59.5, 61.0 (3×OCH_3), 68.2 (C-13), 68.8 (C-5′′′), 74.7 (C-7), 77.3 (C-2′′′), 77.4 (C-11), 81.0 (C-3′′′), 82.0 (C-4′′′), 95.3 (C-1′′′), 116.1 (C-2′′), 116.3 (C-4′′), 118.5 (C-6′′), 130.3 (C-2′), 132.7, 134.4 (C-1, C-2), 133.4 (C-3′′), 136.2 (C-1′), 138.7 (C-1′′), 155.3 (C-5′′), 170.6, 173.6 [C-5, OC(O)CH_3] ppm. MS (DCI): *m/z* (%) = 854.4 (6) [M + NH_4]$^+$. HRMS (ESI) *m/z*: calcd. for $C_{42}H_{65}BrO_{10}Si$: 854.38686 [M + NH_4]$^+$, found 854.38677 [M + NH_4]$^+$.

Analytical Data of 41: R_f = 0.29 (PE/AcOEt, 3:1). $[\alpha]_D^{20}$ = +117.3 (c = 1.0 , in $CHCl_3$). UV (MeCN): λ_{max} (lgε) = 219.5 (4.447), 254.5 (4.230), 299.0 (3.411) nm. IR (film): $\tilde{\nu}$ = 2933, 2856, 1732, 1564, 1462, 1382, 1300, 1245, 1121, 1105, 1033, 1009, 980, 871, 836, 811, 773, 670 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.04, 0.09 (2×s, 2×3 H, SiCH_3), 0.83 (t, J = 7.5 Hz, 3 H, 7-CH_2CH_3), 0.86 [s, 9 H, SiC(CH_3)$_3$], 0.90 (d, J = 6.8 Hz, 3 H, 12-CH_3), 1.23 (d, J = 6.5 Hz, 3 H, 6′′′-H$_3$), 1.20–1.33 (m, 2 H), 1.46–1.54 (m, 3 H), 1.60–1.71 (m, 2 H), 1.74–1.87 (m, 2 H) (8-H$_2$, 9-H$_2$, 10-H$_2$, 12-H, 7-CH_2CH_3), 1.99 [s, 3 H, OC(O)CH_3], 2.51–2.59 (m, 1 H, 4-H$_A$), 2.60–2.69 (m, 2 H, 3a-H, 4-H$_B$), 2.99–3.04 (m, 1 H, 13a-H), 3.12 (m$_c$, 1 H, 3-H), 3.17 (t, J = 9.6 Hz, 1 H, 4′′′-H), 3.54, 3.54, 3.54 (3×s, 9 H, 3×OCH_3), 3.58 (m$_c$, 1 H, 5′′′-H), 3.63 (dd, J = 9.6, 3.4 Hz, 1 H, 3′′′-H), 3.73 (dd, J = 2.8, 1.9 Hz, 1 H, 2′′′-H), 3.97 (d, J = 2.5 Hz, 1 H, 13-H), 4.79 (dd, J = 11.2, 5.3 Hz, 1 H, 7-H), 5.02–5.09 (m, 1 H, 11-H), 5.49 (d, J = 1.9 Hz, 1 H, 1′′′-H), 5.61 (d, J = 5.6 Hz, 1 H), 5.82 (m$_c$, 1 H) (1-H, 2-H), 5.99 (dd, J = 15.6, 9.0 Hz, 1 H, 1′-H), 6.65 (d, J = 15.6 Hz, 1 H, 2′-H), 6.81 (dd, J = 8.7, 2.8 Hz, 1 H, 4′′-H), 7.20 (d, J = 2.8 Hz, 1 H, 6′′-H), 7.40 (d, J = 8.7 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –3.1, –2.9 (2×SiCH_3), 9.2 (C-12-CH_3), 10.0 (C-7-CH_2CH_3), 17.9 (C-6′′′), 18.6 (C-9), 18.7 [SiC(CH_3)$_3$], 21.1 [OC(O)CH_3], 26.2 [SiC(CH_3)$_3$], 28.6, 31.1, 32.0 (C-8, C-10, C-7-CH_2CH_3), 34.5 (C-4), 43.3 (C-12), 44.7 (C-3a), 52.9 (C-13a), 55.1 (C-3), 58.0, 59.4, 61.1 (3×OCH_3), 68.4 (C-13), 68.8 (C-5′′′), 74.7 (C-7), 77.2 (C-2′′′), 77.6 (C-11), 80.9 (C-3′′′), 82.0 (C-4′′′), 95.3 (C-1′′), 114.8 (C-6′′), 115.7 (C-

2′′), 116.7 (C-4′′), 129.2 (C-2′), 132.6, 134.3 (C-1, C-2), 133.6 (C-3′′), 136.1 (C-1′), 137.9 (C-1′′), 155.7 (C-5′′), 170.6, 173.6 [C-5, O*C*(O)CH_3] ppm. MS (DCI): *m/z* (%) = 854.4 (5) $[M + NH_4]^+$. HRMS (ESI) *m/z*: calcd. for $C_{42}H_{65}BrO_{10}Si$: 854.38686 $[M + NH_4]^+$, found 854.38693 $[M + NH_4]^+$.

Compound 45: A solution of **40** (163 mg, 195 µmol, 1.0 equiv.) and *n*Bu_4NOAc (118 mg, 390 µmol, 2.0 equiv.) in DMF/CH_3CN/H_2O (12 mL, 5:5:1) was degassed and Pd-catalyst **43** (12.8 mg, 13.6 µmol, 7.0 mol-%) was added at room temp. The mixture was stirred for 5 min at room temp. and warmed to 125 °C for 1.3 h. Then, the mixture was cooled to room temp., diluted with Et_2O (35 mL) and washed with water (35 mL). The aqueous layer was extracted with Et_2O (2 × 35 mL), the combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 3:1→2.5:1) gave tetracycle **45** (133 mg, 176 µmol, 90%) as a colourless oil.

R_f = 0.25 (PE/AcOEt, 3:1). $[\alpha]_D^{20}$ = +11.3 (*c* = 1.0 , in $CHCl_3$). UV (MeCN): λ_{max} (lg ε) = 222.0 (4.480), 265.0 (3.815), 299.0 (3.278), 274.5 (3.741), 309.0 (3.193) nm. IR (film): ṽ = 2933, 1728, 1603, 1498, 1463, 1369, 1250, 1104, 1048, 1017, 961, 874, 837, 775 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = –0.13, 0.00 (2 × s_{br}, 2 × 3 H, 2 × $SiCH_3$), 0.67–0.94 [m, 15 H, $SiC(CH_3)_3$, 9′′-H_3, 2′′-CH_3], 1.23 (d, *J* = 6.4 Hz, 3 H, 6′′′-H_3), 1.02–1.15 (m, 1 H), 1.16–1.32 (m, 1 H), 1.47–1.86 (m, 7 H) (2′′-H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 8′′-H_2), 1.98 [s, 3 H, OC(O)CH_3], 2.57 (s_{br}, 1 H), 2.72–3.02 (m, 3 H, 2-H_2, 3′-H, 3a′-H), 3.16 (t, *J* = 9.4 Hz, 1 H, 4′′′-H), 3.52, 3.54, 3.54 (3 × s, 3 × 3 H, 3 × OCH_3), 3.61–3.67 (m, 1 H, 5′′′-H), 3.64 (dd, *J* = 9.2, 3.1 Hz, 1 H, 3′′′-H), 3.71 (dd, *J* = 3.3, 2.1 Hz, 1 H, 2′′′-H), 4.07 (s_{br}, 1 H, 9b′-H), 4.22 (s_{br}, 1 H, 1′′-H), 4.92 (s_{br}, 1 H), 5.01 (s_{br}, 1 H) (3′′-H, 7′′-H), 5.49 (d, *J* = 1.4 Hz, 1 H, 1′′′-H), 5.72 (s_{br}, 1 H, 1′-H), 5.90 (s_{br}, 1 H, 4′-H), 6.26 (d, *J* = 9.4 Hz, 1 H, 5′-H), 6.71 (d, *J* = 2.6 Hz, 1 H, 6′-H), 6.81 (dd, *J* = 8.5, 3.0 Hz, 1 H, 8′-H), 7.01 (d, *J* = 8.5 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –5.1, –4.4 (2 × $SiCH_3$), 9.1 (C-2′′-*C*H_3), 10.0 (C-9′′), 17.8 (C-6′′′), 18.2 [Si*C*$(CH_3)_3$], 18.8 (C-5′′), 21.2 [OC(O)*C*H_3], 25.8 [SiC(*C*H_3)$_3$], 28.2, 29.7, 31.1, 31.4 (C-2′′, C-4′′, C-6′′, C-8′′), 37.3, 37.9, 43.8, 50.4 (C-2, C-3′, C-3a′, C-9b′), 57.9, 59.2, 60.9 (3 × OCH_3), 68.5 (C-5′′′), 73.4, 73.6 (C-1′′, C-3′′), 77.4 (C-2′′′), 77.5 (C-7′′), 80.9 (C-3′′′), 82.1 (C-4′′′), 95.2 (C-1′′′), 114.4 (C-6′), 115.5 (C-8′), 126.2, 129.7, 131.4 (C-1′, C-4′, C-5′), 128.5 (C-9′), 129.0, 132.9 (C-2′, C-5a′, C-9a′), 154.8 (C-7′), 170.6, 173.4 [C-1, O*C*(O)CH_3] ppm. MS (DCI): *m/z* (%) = 774.4 (100) $[M + NH_4]^+$. HRMS (ESI) *m/z*: calcd. for $C_{42}H_{64}O_{10}Si$: 774.46070 $[M + NH_4]^+$, found 774.46058 $[M + NH_4]^+$.

Compound 46: To a solution of TBS-protected alcohol **44** (42.0 mg, 55.5 µmol, 1.0 equiv.) in abs. pyridine (2.0 mL) was added at 0 °C HF·pyridine (0.65 mL). The reaction mixture was warmed to 60 °C and stirred for 16 h. Afterwards, the reaction was cooled to room temp., washed with 2 M HCl solution. (2 × 10 mL), sat. $NaHCO_3$ solution. (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 1:1) yielded alcohol **46** (28.5 mg, 44.3 µmol, 80%) as a white solid.

R_f = 0.30 (PE/AcOEt, 1:1). $[\alpha]_D^{20}$ = –158.7 (*c* = 0.75 , in $CHCl_3$). UV (MeCN): λ_{max}(lg ε) = 226.0 (4.432), 257.0 (3.714), 265.0 (3.789), 274.5 (3.686), 298.5 (3.259) nm. IR (film): ṽ = 2929, 1730, 1602, 1499, 1463, 1375, 1249, 1103, 1016, 874 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3 H, 9′′-H_3), 0.90 (d, *J* = 6.6 Hz, 3 H, 2′′-CH_3), 1.23 (d, *J* = 6.0 Hz, 3 H, 6′′′-H_3), 1.15–1.41 (m, 2 H), 1.47–1.72 (m, 6 H), 1.77–1.86 (m, 1 H), (4′′-H_2, 5′′-H_2, 6′′-H_2, 8′′-H_2, OH), 2.02 [s, 3 H, OC(O)CH_3], 2.05–2.12 (m, 1 H, 2′′-H), 2.59 (dd, *J* = 15.0, 5.4 Hz, 1 H, 2-H_A), 2.81 (dd, *J* = 15.0, 4.0 Hz, 1 H, 2-H_B), 3.11–3.19 (m, 2 H, 3′-H, 4′′′-H), 3.39–3.46 (m, 1 H, 3a′-H), 3.51, 3.53, 3.54 (3 × s, 9 H, 3 × OCH_3), 3.59–3.67 (m, 2 H, 3′′′-H, 5′′′-H), 3.70 (m, 1 H, 2′′′-H), 4.15 (d, *J* = 9.6 Hz, 1 H, 9b′-H), 4.25 (s, 1 H, 1′′-H), 4.72 (m_c, 1 H, 7′′-H), 4.94 (m_c, 1 H, 3′′-H), 5.47 (s, 1 H, 1′′′-H), 5.69 (s, 1 H, 1′-H), 5.83 (dd, *J* = 9.6, 3.6 Hz, 1 H, 4′-H), 6.23 (d, *J* = 9.6 Hz, 1 H, 5′-H), 6.69 (d, *J* = 2.4 Hz, 1 H, 6′-H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 1 H, 8′-H), 7.00 (d, *J* = 8.4 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 9.6 (C-9′′), 10.5 (C-2′′-*C*H_3), 17.8 (C-6′′′), 20.0 (C-5′′), 21.1 [OC(O)-*C*H_3], 27.9, 30.3, 31.8 (C-4′′, C-6′′, C-8′′), 37.5 (C-2), 38.2 (C-2′′), 43.9 (C-3a′), 44.2 (C-9b′), 51.5 (C-3′), 57.9, 59.2, 60.9 (3 × OCH_3), 68.5 (C-5′′′), 69.1 (C-1′′), 75.9 (C-3′′), 77.3 (C-2′′′), 77.5 (C-7′′), 80.8 (C-3′′′), 82.0 (C-4′′′), 95.2 (C-1′′′), 114.7 (C-6′), 115.1 (C-8′), 125.6 (C-5′), 128.4 (C-9a′*), 128.6 (C-9′), 131.0 (C-4′), 132.1 (C-1′), 133.0 (C-5a′*), 145.5 (C-2′), 155.1 (C-7′), 170.8, 172.2 [C-1, O*C*(O)CH_3] ppm. MS (DCI): *m/z* (%) = 660.4 (8) $[M + NH_4]^+$, 642.4 (100) $[M]^+$. HRMS (ESI) *m/z*: calcd. for $C_{36}H_{50}O_{10}$: 665.32962 $[M + Na]^+$, found 665.32967 $[M + NH_4]^+$.

Spinosyn Analogue 3a: To a solution of acetate **46** (45.9 mg, 71.4 µmol, 1.0 equiv.) in abs. MeOH (4.5 mL) was added at 0 °C K_2CO_3 (9.87 mg, 71.4 µmol, 1.0 equiv.), and the mixture was stirred for 2.5 h at 0 °C and 4.0 h at room temp. The reaction was quenched with sat. NH_4Cl-sol. (5 mL) and H_2O (20 mL) and the mixture extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 1:1) yielded diol **3a** (28.4 mg, 44.3 µmol, 66% yield, 86% brsm) as a white solid. R_f = 0.16 (PE/AcOEt, 1:1); ^1H NMR (600 MHz, $CDCl_3$): δ = 0.83–0.90 (m, 6 H, 9′′-H_3, C-2′′-H_3), 1.23 (d, *J* = 6.3 Hz, 3 H, 6′′′-H_3), 1.20–1.38 (m, 1 H), 1.45–1.54 (m, 1 H), 1.55–1.74 (m, 5 H), 1.86 (m_c, 2 H), (2′′-H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 8′′-H_2), 1.98 (s_{br}, 1 H, 1′′-OH), 2.36 (s_{br}, 1 H, 3′′-OH), 2.48 (dd, *J* = 17.0, 9.3 Hz, 1 H, 2-H_A), 2.73 (dd, *J* = 17.0, 3.0 Hz, 1 H, 2-H_B), 3.02–3.08 (m, 1 H, 3′-H), 3.12–3.17 (m, 1 H, 3a′-H), 3.16 (t, *J* = 9.6 Hz, 1 H, 4′′′-H), 3.51, 3.53, 3.54 (3 × s, 9 H, 3 × OCH_3), 3.60–3.66 (m, 2 H, 3′′′-H, 5′′′-H), 3.69–3.72 (m, 1 H, 2′′′-H), 3.90 (m_c, 1 H, 3′′-H), 4.12 (d, *J* = 9.6 Hz, 1 H, 9b′-H), 4.28 (m_c, 1 H, 7′′-H), 4.37 (s_{br}, 1 H, 1′′-H), 5.47 (d, *J* = 1.5 Hz, 1 H, 1′′′-H), 5.79 (s_{br}, 1 H, 1′-H), 5.83 (dd, *J* = 10.0, 4.1 Hz, 1 H, 4′-H), 6.24 (d, *J* = 10.0 Hz, 1 H, 5′-H), 6.69 (d, *J* = 2.6 Hz, 1 H, 6′-H), 6.84 (dd, *J* = 8.1, 2.6 Hz, 1 H, 8′-H), 7.03 (d, *J* = 8.6 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.8, 10.4 (C-9′′, C-2′′-*C*H_3), 17.8 (C-6′′′), 20.0, 27.0, 28.8, 32.1 (C-4′′, C-5′′, C-6′′, C-8′′), 36.5 (C-2′′), 38.4 (C-2′′), 43.8 (C-9b′), 44.9 (C-3a′), 51.1 (C-3′), 57.9, 59.2, 60.9 (3 × OCH_3), 68.5 (C-5′′′), 74.6 (C-1′′), 74.8 (C-3′′), 77.3 (C-2′′′), 80.9 (C-3′′′), 81.0 (C-7′′), 82.0 (C-4′′′), 95.2 (C-1′′′), 114.7 (C-6′), 115.3 (C-8′), 125.9 (C-5′), 128.6, 128.6 (C-9′, C-9a′*), 130.3, 130.4 (C-1′, C-4′), 132.9 (C-5a′*), 147.2 (C-2′), 155.1 (C-7′), 171.9 (C-1) ppm. MS (DCI): *m/z* (%) = 618.4 (100) $[M + NH_4]^+$. HRMS (ESI) *m/z*: calcd. for $C_{34}H_{48}O_9$ 623.31905 $[M + Na]^+$, found 623.31924 $[M + Na]^+$.

Compound 47: To a solution of TBS-protected alcohol **45** (126 mg, 166 µmol, 1.0 equiv.) in abs. pyridine (5.9 mL) was added at 0 °C HF·pyridine (1.96 mL). The reaction mixture was warmed to 60 °C and stirred for 15.5 h. Afterwards it was cooled to room temp., washed with 2 M HCl solution. (2 × 25 mL), sat. $NaHCO_3$ solution. (25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 1:1→2:3) yielded alcohol **47** (103 mg, 160 µmol, 96%) as a light brown solid. R_f = 0.37 (PE/AcOEt, 1:1). $[\alpha]_D^{20}$ = +56.8 (*c* = 0.5 , in

$CHCl_3$). UV (MeCN): λ_{max} (lgε) = 222.5 (4.428), 225.5 (4.428), 256.5 (3.739), 264.5 (3.806), 274.5 (3.705), 299.5 (3.282) nm. IR (film): $\tilde{\nu}$ = 2928, 1725, 1603, 1499, 1463, 1370, 1248, 1138, 1102, 1047, 1015, 874, 801, 663 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.66 (d, J = 6.8 Hz, 3 H, 2′′-CH_3), 0.85 (t, J = 7.5 Hz, 3 H, 9′′-H_3), 1.24 (d, J = 6.2 Hz, 3 H, 6′′′-H_3), 1.16–1.29 (m, 1 H), 1.34–1.43 (m, 1 H), 1.44–1.60 (m, 4 H), 1.78–1.90 (m, 4 H) (2′′-H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 8′′-H_2, OH), 1.99 [s, 3 H, OC(O)CH_3], 2.49 (dd, J = 14.1, 9.0 Hz, 1 H, 2-H_A), 2.67 (d, J = 14.1 Hz, 1 H, 2-H_B), 2.88–2.96 (m, 2 H, 3′-H, 3a′-H), 3.16 (t, J = 9.3 Hz, 1 H, 4′′′-H), 3.52, 3.53, 3.54 (3 × s, 9 H, 3 × OCH_3), 3.60–3.67 (m, 2 H, 3′′′-H, 5′′′-H), 3.71 (s_{br}, 1 H, 2′′′-H), 4.02 (d, J = 9.5 Hz, 1 H, 9b′-H), 4.43 (s_{br}, 1 H, 1′′-H), 4.87–5.00 (m, 2 H, 3′′-H, 7′′-H), 5.48 (s_{br}, 1 H, 1′′′-H), 5.76 (s_{br}, 1 H, 1′-H), 5.88 (dd, J = 9.8, 3.7 Hz, 1 H, 4′-H), 6.29 (d, J = 9.8 Hz, 1 H, 5′-H), 6.72 (d, J = 2.5 Hz, 1 H, 6′-H), 6.82 (dd, J = 8.2, 2.5 Hz, 1 H, 8′-H), 7.02 (d, J = 8.2 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 7.9 (C-2′′-*C*H_3), 9.9 (C-9′′), 17.8 (C-6′′′), 18.4 (C-5′′), 21.1 [OC(O)*C*H_3], 28.2, 31.3, 32.8 (C-4′′, C-6′′, C-8′′), 36.5 (C-2′′), 39.5 (C-2), 43.7 (C-9b′), 47.2, 50.7 (C-3′, C-3a′), 57.9, 59.2, 60.9 (3 × OCH_3), 68.5 (C-5′′′), 70.6 (C-1′′), 75.5 (C-7′′), 77.2, 77.3 (C-3′′, C-2′′′), 80.9 (C-3′′′), 82.0 (C-4′′′), 95.2 (C-1′′′), 114.4 (C-6′), 115.5 (C-8′), 126.5 (C-5′), 128.5 (C-9′), 128.6 (C-9a′*), 129.1 (C-1′), 129.8 (C-4′), 132.9 (C-5a′*), 148.0 (C-2′), 155.1 (C-7′), 171.0, 174.1 [C-1, O*C*(O)-CH_3] ppm. MS (DCI): m/z (%) = 660.5 (100) $[M + NH_4]^+$. HRMS (ESI) m/z: calcd. for $C_{36}H_{50}O_{10}$ 665.32962 $[M + Na]^+$, found 665.32954 $[M + Na]^+$.

Spinosyn Analogue 3b: To a solution of acetate **47** (71.3 mg, 110 µmol, 1.0 equiv.) in abs. MeOH (7.0 mL) was added at 0 °C K_2CO_3 (15.3 mg, 110 µmol, 1.0 equiv.), and the mixture was stirred for 80 min at 0 °C and 4.0 h at room temp. The reaction was quenched with sat. NH_4Cl-sol. (5 mL) and H_2O (15 mL) and the mixture extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Purification of the residue by column chromatography on silica gel (PE/AcOEt, 1:1) yielded diol **3a** (53.5 mg, 89.1 µmol, 81% yield, 90% brsm) as a white solid. R_f = 0.12 (PE/AcOEt, 1:1). $[\alpha]_D^{20}$ = +51.7 (c = 0.6, in $CHCl_3$). UV (MeCN): λ_{max} (lgε) = 222.0 (4.450), 257.0 (3.726), 264.5 (3.801), 274.5 (3.727), 299.5 (3.264), 309.0 (3.184) nm. IR (film): $\tilde{\nu}$ = 3474, 2934, 1721, 1603, 1498, 1462, 1365, 1252, 1101, 1048, 1015, 875, 800 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.60 (d, J = 7.1 Hz, 3 H, 2′′-CH_3), 0.84 (t, J = 7.3 Hz, 3 H, 9′′-H_3), 1.24 (d, J = 6.4 Hz, 3 H, 6′′′-H_3), 1.06–1.14 (m, 1 H), 1.38–1.74 (m, 7 H), 1.75–1.84 (m, 1 H) (2′′-H, 4′′-H_2, 5′′-H_2, 6′′-H_2, 8′′-H_2), 1.89–2.04 (m, 1 H, OH), 2.21–2.32 (m, 1 H, OH), 2.46 (dd, J = 14.2, 9.3 Hz, 1 H, 2-H_A), 2.59 (d, J = 14.2 Hz, 1 H, 2-H_B), 2.76–2.82 (m, 1 H, 3a′-H), 2.82–2.87 (m, 1 H, 3′-H), 3.17 (t, J = 9.5 Hz, 1 H, 4′′′-H), 3.52, 3.54, 3.54 (3 × s, 9 H, 3 × OCH_3), 3.62–3.68 (m, 2 H, 3′′′-H, 5′′′-H), 3.70–3.73 (m, 1 H, 2′′′-H), 3.94–4.00 (m, 2 H, 9b′-H, 3′′-H), 4.56 (s_{br}, 1 H, 1′′-H), 4.90 (m_c, 1 H, 7′′-H), 5.49 (d, J = 1.7 Hz, 1 H, 1′′′-H), 5.99 (s_{br}, 1 H, 1′-H), 6.03 (dd, J = 9.8, 4.9 Hz, 1 H, 4′-H), 6.35 (d, J = 9.8 Hz, 1 H, 5′-H), 6.75 (d, J = 2.4 Hz, 1 H, 6′-H), 6.81 (dd, J = 8.3, 2.4 Hz, 1 H, 8′-H), 7.02 (d, J = 8.3 Hz, 1 H, 9′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 4.5 (C-2′′-*C*H_3), 9.9 (C-9′′), 17.8 (C-6′′′), 19.4 (C-5′′), 28.3, 31.9, 33.5 (C-4′′, C-6′′, C-8′′), 35.6 (C-2′′), 37.9 (C-2), 43.0 (C-9b′), 47.3 (C-3a′), 50.4 (C-3′), 57.8, 59.1, 60.9 (3 × OCH_3), 68.5 (C-5′′′), 74.1 (C-3′′), 74.6 (C-1′′), 77.3 (C-2′′′), 78.0 (C-7′′), 80.8 (C-3′′′), 82.0 (C-4′′′), 95.2 (C-1′′′), 114.3 (C-6′), 115.7 (C-8′), 127.4 (C-5′), 127.5 (C-1′), 128.2 (C-9′), 128.6 (C-4′), 129.0 (C-9a′*), 133.1 (C-5a′*), 148.4 (C-2′), 154.9 (C-7′), 174.2 (C-1) ppm. MS (DCI): m/z (%) = 618.6 (100) $[M + NH_4]^+$, 600.6 (2) $[M + H]^+$. HRMS (ESI) m/z: calcd. for $C_{34}H_{48}O_9$ 623.31905 $[M + Na]^+$, found 623.31926 $[M + Na]^+$.

Supporting Information (see footnote on the first page of this article): Synthetic procedures for all new compounds as well as copies of the ^1H and ^{13}C NMR spectra of the key intermediates and final products as well as the X-ray crystal structure.

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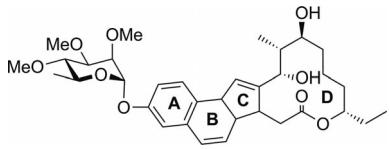
Total Synthesis

The natural spinosyns A and D are highly potent insecticides, but there is a great demand for analogues to overcome resistance.



Keywords: Total synthesis / Natural products / Macrolactones / Heck reaction / Cyclization / Spinosyns / Insecticides / Crop protection

