COMMUNICATION

Chemoenzymatic approaches to the decahydro-*as*-indacene cores associated with the spinosyn class of insecticide

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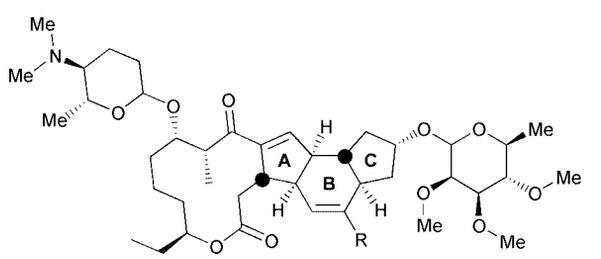
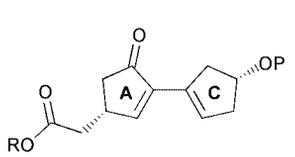
The enantiopure dienes 8 and 24, which have been prepared by chemoenzymatic methods, engage in Diels–Alder cycloaddition reactions with maleic and citraconic anhydride to give adducts (*e.g.* 25–27) embodying the ABC-ring system associated with spinosyns A (1) and D (2).

Controlling insect pests is essential to maintaining high agricultural productivity and to minimising monetary losses. The discovery of new and improved pesticides is necessitated by increased pest resistance toward existing products as well as the stricter environmental and toxicological regulations now being introduced world-wide.[1] During the 1980's the soil micro-organism *Saccharopolyspora spinosa* was shown to produce a family of macrolides of which the primary components are spinosyn A (**1**) [a.k.a. (−)-lepicidin A] and spinosyn D (**2**).[2] Spinosad™ (a.k.a. Tracer™), which is one of the trade-names for the mixture of compounds (**1**) and (**2**) now produced



1 R = H
2 R = Me



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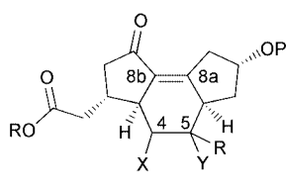

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commercially by fermentation methods, has proven effective in controlling many chewing insect pests such as caterpillars, leafminers, worms, flies and beetles that attack cotton, trees, fruits, vegetables, turf and ornamentals. Although its mode of action is not fully understood, Spinosad™ appears to affect nicotinic acetylcholine and γ-aminobutyric acid (GABA) receptors through a novel mechanism.[3] Further, Spinosad™ displays relatively low toxicity in mammals as well as birds and, as such, has been designated a reduced-risk pesticide by the Environmental Protection Agency in the USA.[4]

The biological and commercial significance of the spinosyns together with their challenging molecular architectures have prompted a number of synthetic studies.[5–7] Thus far, two total syntheses of spinosyn A have been reported, one by the Evans group at Harvard (in 1993)[6] and the other by the Paquette group at Ohio State (in 1998).[7] In this connection we now outline convergent and chemoenzymatic methods for the diastereoselective construction of enantiopure decahydro-*as*-indacenes related to the ABC-ring system of compounds **1** and **2**.

The pivotal feature associated with our approach to the decahydro-*as*-indacene ring-system involves a diastereofacially selective intermolecular Diels–Alder cycloaddition reaction[8] between a diene such as **3** and a dienophile [(X)CH=CR(Y) wherein R = H or Me] which can, ultimately, act as a synthetic equivalent for acetylene or propyne.[9] The $\Delta^{8a,8b}$-double bond (*as*-indacene numbering) associated with the expected adduct **4** would then be removed, perhaps *via* 1,4-reduction involving a hydride source.[10] Subsequent elimination of the groups X and Y would be employed to establish the $\Delta^{4,5}$-double bond associated with the target.

To test such ideas a model study involving diene **8** was carried out (Scheme 1). This 4π-addend was prepared by converting the known[11] cyclopentenone **5**, itself available *via* chemoenzymatic techniques from cyclopentadiene, into the corresponding cyclopentenyl triflate **6**† {70%, $[a]_D$ +2.2 [*c* 0.8]‡} using conditions described by Paquette[7a] for the synthesis of *ent*-**6** {lit.[7a] $[a]_D$ −1.7 (*c* 0.8, $CHCl_3$)}. Treatment of the cyclopentenyl bromide **7**[12] with *tert*-butyllithium and transmetallation of the resulting cyclopentenyllithium with anhydrous zinc chloride afforded the corresponding organozinc chloride. This was subjected to a Negishi cross-coupling reaction[13] with triflate **6** in the presence of $Pd(PPh_3)_4$ to give, after acidic work up with aqueous oxalic acid, the target diene **8** {72%, mp = 49–50 °C, $[a]_D$ −17 (*c* 1.1)}. We viewed maleic anhydride (**9**) and citraconic anhydride (**10**) as the most appropriate synthetic equivalents for acetylene and propyne, respectively, since their Diels–Alder adducts (or the derived *vic*-diacids) can be decarboxylated under a variety of conditions to give the corresponding alkenes.[14] While compound **8** failed to participate in a thermally promoted Diels–Alder reaction with either anhydride **9** or **10**, when a 1:1 molar mixture of these reaction partners was subjected (as a dichloromethane solution), to 19 kbar§ at 18 °C for 2 h the expected adducts were formed. Thus, diene **8** reacted with maleic anhydride to give compound **11** {33%, mp = 183–185 °C, $[a]_D$ −59 (*c* 0.8)} as the only characterisable product. Reaction of compound **8** with citraconic anhydride afforded a *ca.* 1:1 mixture of the regioisomeric adducts **12** {29%, mp = 155–157 °C, $[a]_D$ −117 (*c* 0.9)} and **13** {30%, mp = 145–147 °C, $[a]_D$ +14 (*c* 1.0)} which could be separated from one another by flash chromatography. Single-crystal X-ray analysis of adduct **13**¶ (Fig. 1) served to confirm the illustrated structure and highlight the strong steric effect that is being exerted by the *tert*-butyldimethylsiloxy group within compound **8** in terms of directing dienophilic attack to the β-face of this diene.

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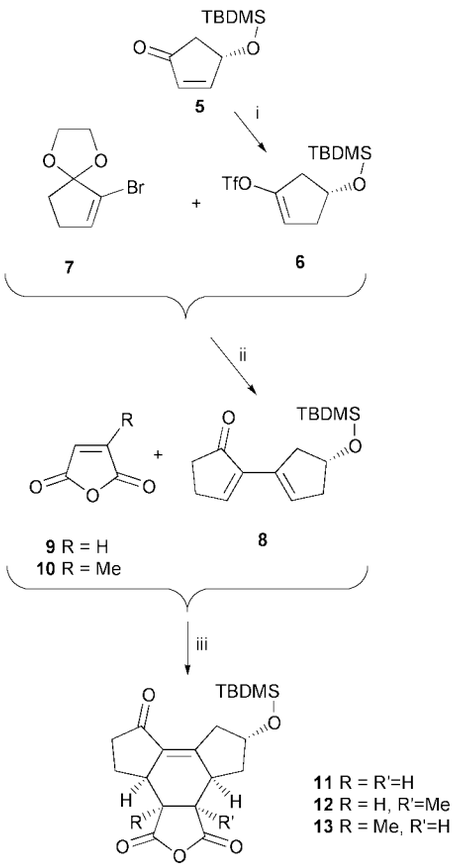


Scheme 1 *Reagents and conditions*: (i) L-Selectride™ (1.0 M solution in THF, 1 mol equiv.), Et_3N, THF, −78 °C, *ca*. 0.5 h then *N*-phenyltriflimide (0.9 mol equiv.), −78 to 18 °C, 3 h; (ii) *t*-BuLi (2.0 mol equiv. wrt compound **7**), THF, −78 to −60 °C, *ca*. 0.5 h then $ZnCl_2$ (1 mol equiv.), THF, −78 to 0 °C, 1.0 h then compound **6** (1.0 mol equiv.), $Pd(PPh_3)_4$ (cat.), 18 °C, 1 h then aqueous oxalic acid, CH_2Cl_2, EtOH (trace); (iii) compound **9** or **10** (*ca*. 1.3 mol equiv.), CH_2Cl_2, 19 kbar, 18 °C, 2 h.

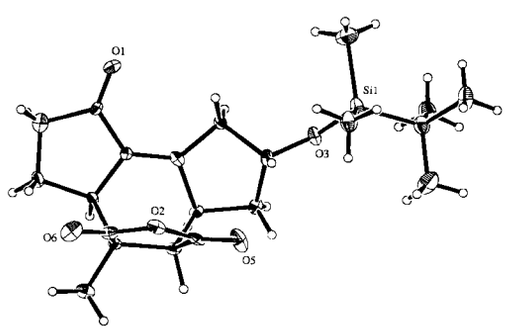
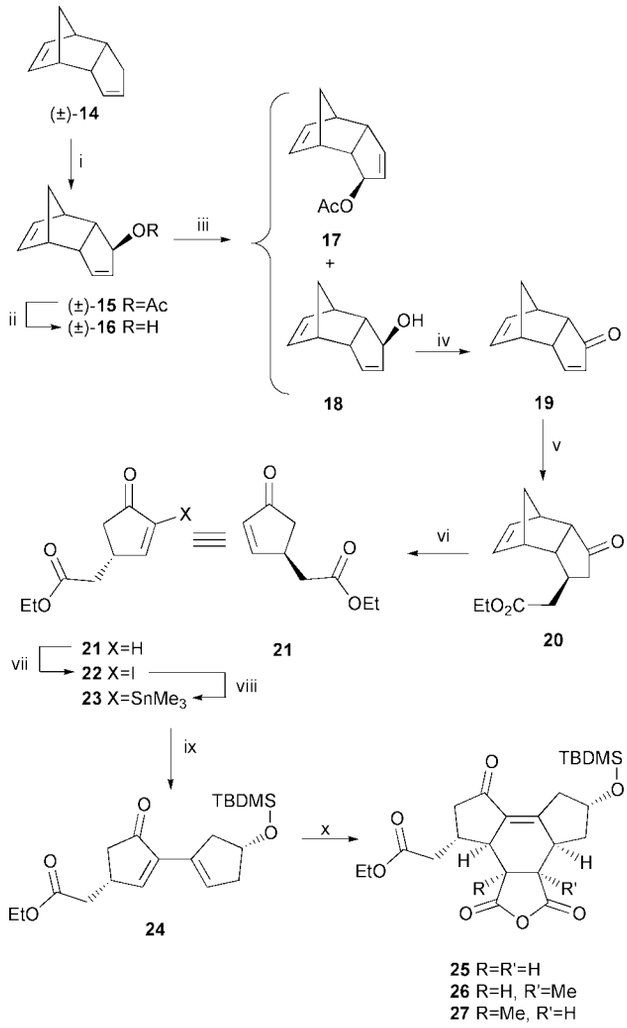


Fig. 1 ORTEP diagram of compound **13** derived from X-ray crystallographic data.

Encouraged by the above mentioned model studies, we next sought to incorporate an acetic acid side-chain into the diene so as to construct a substrate of the general type **3**. To these ends (Scheme 2) dicyclopentadiene [(±)-**14**] was subjected to allylic acetoxylation using manganese triacetate and the racemic mixture of acetates (±)-**15**[15] thus formed was hydrolysed to the corresponding mixture of alcohols (±)-**16**.[15] Subjection of the latter mixture to kinetic enzymatic resolution by treatment with lipase PS (*Pseudomonas* sp.) (*ex* Amano Pharmaceutical Co. Ltd‖)[16] in the presence of vinyl acetate afforded a *ca*. 1:1 mixture of acetate **17** (44%, 74% ee**) and alcohol **18** (39%, 72% ee) which were readily separated from one another by flash chromatography. The latter product was oxidised, with PCC, to the corresponding ketone which was subjected to recrystallisation three times from hexane. In this manner enantiomerically pure enone **19**[15] {65%, mp = 76–76.5 °C, $[a]_D$ +142 (*c* 2.1)} was obtained. Conjugate addition of magnesium monoethyl



Scheme 2 *Reagents and conditions*: (i) $Mn(OAc)_3$ (1.1 mol equiv.), KBr (cat.), AcOH, 70 °C, 1 h; (ii) K_2CO_3 (1.0 mol equiv.), MeOH, 18 °C, 24 h; (iii) lipase PS (*Pseudomonas cepacia*, 0.1 g $mmol^{-1}$ substrate), vinyl acetate (10.0 mol equiv.), C_6H_6, 28 °C, 14 days; (iv) PCC (1.5 mol equiv.), CH_2Cl_2, 18 °C, 3 h; (v) magnesium monoethyl malonate (1.4 mol equiv.), DMF, 60 °C, 2 d then AcOH (3.2 mol equiv.), 85 °C, 24 h; (vi) 1,2-dichlorobenzene, 180 °C, 3 h; (vii) I_2 (4.2 mol equiv.), 1:1 v/v CCl_4–pyridine, 0 to 18 °C, 24 h; (viii) Me_6Sn_2 (1.0 mol equiv.), $Pd(PPh_3)_4$ (cat.), LiCl (3.0 mol equiv.), THF, reflux, 4 h; (ix) compound **6** (1.0 mol equiv.), $Pd_2dba_3{\cdot}CHCl_3$ (cat.), LiCl (3.0 mol equiv.), *N*-methylpyrrolidinone, 18 °C, 16 h; (x) compound **9** or **10** (*ca*. 1.3 mol equiv.), CH_2Cl_2, 19 kbar, 18 °C, 2 h.

malonate[17] to compound **19** proceeded in a completely diastereofacially selective fashion involving nucleophilic attack at the *exo*-face of the Michael acceptor. The initially formed Michael adduct was subjected to acidic work-up which effected decarboxylation and, thereby, formation of keto-ester **20** {72%, $[a]_D$ +119 (*c* 1.0)}. Heating the latter compound in 1,2-dichlorobenzene at reflux resulted in a retro-Diels–Alder reaction and formation of the cyclopentenone **21** {97%, $[a]_D$ +113 (*c* 1.5)} which was subjected to *a*-iodination under conditions defined by Johnson *et al.*[18] Compound **22** {65%, $[a]_D$ +19 (*c* 1.1)} formed in this manner was then subjected to stannylation with hexamethylditin in the presence of $Pd(PPh_3)_4$ and in this way the desired stannane **23** {49%, $[a]_D$ +55 (*c* 2.0)} was obtained. Stille type cross-coupling of the latter compound with triflate **6** in the presence of tris(dibenzylideneacetone)-dipalladium(0)–chloroform ($Pd_2dba_3{\cdot}CHCl_3$, *ex* Aldrich)[19] then afforded the required diene **24** {65%, $[a]_D$ +22 (*c* 0.8)}. At 19 kbar compound **24** engaged in a Diels–Alder cycloaddition reaction with dienophile **9** to afford, as the only characterisable product of reaction, adduct **25** {44%, mp = 140–141 °C, $[a]_D$ −50 (*c* 1.2)}. This product was accompanied by significant quantities of an insoluble black powder which is presumed to result from polymerisation of the diene **24**. The assignment

of the illustrated stereochemistry within compound **25** is by analogy with the outcomes of the Diels–Alder reactions involving the model compound **8**. Reaction of diene **24** with citraconic anhydride under the same high pressure conditions afforded a 1:1 mixture (56% combined yield) of adducts **26** {mp = 147–148 °C, $[\alpha]_D$ −133 (*c* 0.6)} and **27** {mp = 94–95 °C, $[\alpha]_D$ −26 (*c* 0.6)} which were separated by fractional crystallisation from diethyl ether.†† These materials were again accompanied by significant amounts of polymeric material as well as *ca*. 5–10% of a dimeric species derived (*via* a Diels–Alder reaction?) from compound **24**.

The foregoing results clearly demonstrate that chemoenzymatic techniques allow for the ready preparation of dienes **8** and **24**. Furthermore, such compounds participate in diastereofacially selective Diels–Alder reactions with anhydrides **9** and **10** so as to deliver decahydro-*as*-indacenes relevant to the construction of spinosyins A and D as well as certain biologically active analogues.[20] Simple variations on the above mentioned procedures would enable construction of the enantiomeric series of decahydro-*as*-indacenes as required in ikarugamycin[5] and capsimycin.[5] The present work is also relevant to assembly of the *as*-indacene core associated with the potent new antimitotic agent WS9885B (a.k.a. FR182877).[21]

Experimental

Ethyl {(1′*S*)-3′-[(4″*R*)-4″-*tert*-butyldimethylsiloxycyclopenten-1″-yl]-4′-oxocyclopent-2′-enyl}acetate (24)

A mixture of stannane **23** (475 mg, 1.43 mmol), triflate **6** (497 mg, 1.43 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (40 mg, 0.039 mmol) and dry LiCl (181 mg, 4.30 mmol) in *N*-methylpyrrolidinone (3 mL) was stirred at 18 °C for 16 h. The reaction mixture was diluted with water (60 mL) then extracted with ether (3 × 60 mL). The combined organic extracts were washed with KF (1 × 60 mL of a saturated aqueous solution) and brine (1 × 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 ethyl acetate–hexane elution) and concentration of the appropriate fractions (R_f = 0.6) afforded the *title compound* **24** (340 mg, 65%) as a pale-yellow oil, $[\alpha]_D$ +22 (*c* 0.8, $CHCl_3$) [Found: $M^{+\bullet}$, 364.2065. $C_{20}H_{32}O_4Si$ requires $M^{+\bullet}$, 364.2070]. ν_{max} (KBr plates/cm^{-1}) 1735, 1711; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (br d, *J* = 2.6 Hz, 1H), 6.69 (br s, 1H), 4.54 (septet, *J* = 3.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.33–3.44 (complex m, 1H), 2.73–2.79 (complex m, 3H), 2.40–2.50 (complex m, 4H), 2.15 (dd, *J* = 18.9 and 2.6 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 171.6, 157.8, 139.7, 130.8, 129.8, 71.5, 60.8, 44.0, 43.6, 42.3, 39.3, 34.8, 26.0, 18.3, 14.3, −4.70; *m/z* (EI, 70 eV) 364 (10%, $M^{+\bullet}$), 307 [100, $(M - C_4H_9^{\bullet})^+$].

Acknowledgements

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Notes and references

† All new and stable compounds had spectroscopic data [IR, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ All optical rotations were determined in chloroform solution at 20 °C.

§ High pressure reactions were carried out using a PSIKA 20 kbar High Pressure Reactor purchased from PSIKA Pressure Systems Ltd, Lambert House, Brook St, Glossop, Derbyshire, UK SK13 8BG.

¶ *Crystal data for* **13**: $C_{21}H_{30}O_5Si$, *M* = 390.55, *T* = 173(1) K, monoclinic, space group $P2_1$ (#4), *Z* = 2, *a* = 6.423(3), *b* = 11.868(3), *c* = 14.006(3) Å, *U* = 1065.9(6) Å^3, μ(CuKα) = 11.8 cm^{-1}, 1687 unique data ($2\Theta_{max}$ = 120.2°), 1192 with $I > 3\sigma(I)$; *R* = 0.058, *Rw* = 0.057, S = 2.41.

Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.54180 Å). Refinement was by full-matrix least squares analysis on *F* using the teXsan structure analysis software of Molecular Structure Corporation.[22] Structure solution was by direct methods (SIR92).[23] The absolute configuration of compound **13** follows from its synthesis using building blocks of known chirality. CCDC reference number 207/483. See http://www.rsc.org/suppdata/p1/b0/b006759h/ for crystallographic files in .cif format.

‖ See http://www.amano-enzyme.co.jp.

** Enantiomeric excesses (ee) were determined by chiral GLC analysis [using a 25QC2/CYDEX-B 0.25 capillary column supplied by SGE International Pty Ltd (E-mail: info@sge.com.au)] of compounds **17** and **19**.

†† The higher melting member of this pair of regioisomeric products (which was also less soluble in diethyl ether) is tentatively assigned as compound **26**. By default, then, the lower melting isomer is assigned structure **27**. These assignments derive from a comparison of the ^{1}H NMR chemical shift data for the oxymethine hydrogen and the angular methyl group hydrogens in these compounds with the shifts of their counterparts in compounds **12** and **13** (and for which structures have been established by X-ray crystallographic techniques). The relevant chemical shifts are δ 4.51 and 1.56 (compound **12**), 4.59 and 1.59 (compound **13**), 4.50 and 1.56 (compound **26**), 4.59 and 1.63 (compound **27**).

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