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THE TOTAL SYNTHESIS OF (±)-TRICHOSTATIN A

SOME OBSERVATIONS ON THE ACYLATION AND ALKYLATION OF SILYL ENOL ETHERS, SILYL DIENOL ETHERS AND A SILYL TRIENOL ETHER

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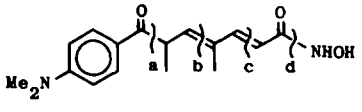
Abstract—Two successful synthetic routes to trichostatin A (**1**) are described; one (Scheme 2) uses the γ-alkylation of a silyl dienol ether, the other (Scheme 4) uses a silyl-protected cyanohydrin anion. The two routes bear an umpolung relation to each other. The Lewis acid-catalysed acylation of silyl enol ethers is a simple and effective way to prepare β-diketones and β-keto esters (Scheme 1); this reaction however gave only α-acylation of the silyl trienol ether (**11**) (Scheme 3), and the silyl trienol ether (**11**) had to be prepared by a round-about route (Scheme 3).

Mukaiyama and Ishida[1] and we[2,3] have reported that silyl dienol ethers are attacked by electrophiles mainly at the γ-position, in contrast to the corresponding lithium dienolates, which are attacked mainly at the α-position. We saw an opportunity to put this selectivity to use in a synthesis of trichostatin A (**1**) an antifungal compound from some strains of *Streptomyces hygroscopicus*.[4]



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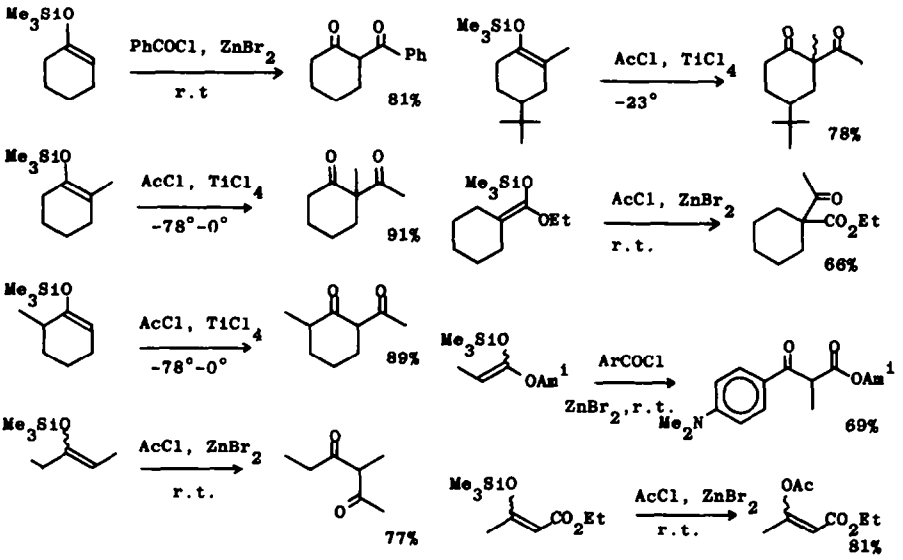
The overall synthetic plan for such a compound is, in a sense, obvious, and consists simply in putting the disconnections *a–d* into practice. The step corresponding to *d* is likely to be done last, but there is some flexibility in the order for the steps corresponding to *a*, *b* and *c*. Since the steps corresponding to *b* and *c* are aldol and Wittig reactions, the most interesting step is that corresponding to *a*. In one sense, the most obvious way to carry out this step would be to acylate a silyl enol ether.

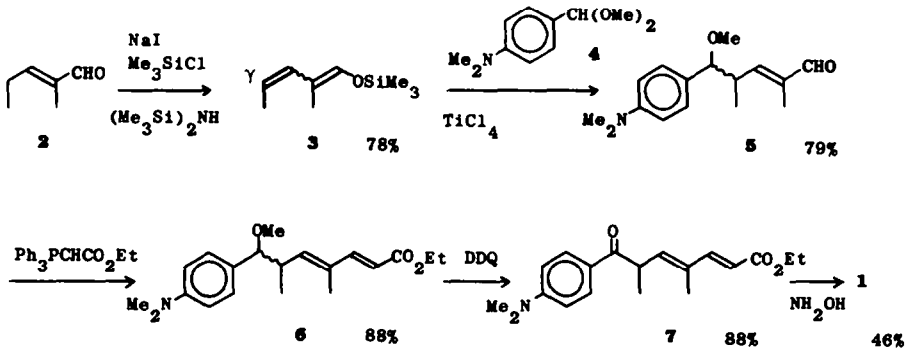
The acylation of silyl enol ethers. The acylation of silyl enol ethers has been reported from time to time. Acid chlorides react without catalysis only with rather specially reactive silyl enol ethers,[5] or when oxalyl chloride[6] or chlorinated acid chlorides[7] are used. Triethylamine catalysis (presumably generating ketenes) can be used with acid chlorides and some ester-derived silyl enol ethers.[8] Fluoride ion catalysis with ethoxycarbonyl fluoride leads to O-acylation,[9] as does catalysis with mercuric salts and acid chlorides.[10] Trimethylsilyl triflate catalysis allows acid anhydrides to be used;[11] and acyl fluorborates are reactive enough not to need catalysis at all.[11] In spite of all this work, Lewis acid-catalysis of the reaction of acid chlorides with silyl enol ethers has barely been mentioned.[3,13] We began, therefore, with an investigation of the feasibility of this simple method for the synthesis of β-dicarbonyl compounds. Our results are summarised in Scheme 1. They show that the reaction is regiospecific, and amenable to the synthesis of enolisable and non-enolisable β-dicarbonyl systems, but only when the silyl enol ether is derived from a ketone or an ester. O-Acylation was observed with the silyl enol ether derived from acetoacetate (as illustrated) and we got signs of O-acylation from the silyl enol ethers derived from aldehydes. Clearly, except for these limitations, it is a good method for the regiospecific synthesis of β-diketones and β-ketoesters. However, we were not in the event able to use it for the synthesis of trichostatin A.

Route 1. We tried the acylation of the silyl dienol ether **3** derived from the aldol condensation product (**2**) of propionaldehyde. As with our earlier attempts to acylate the silyl enol ethers of aldehydes, this failed. However, we easily got round this difficulty by using the acetal **4**, which gave the ether **5** in a Mukaiyama reaction.[1] A Wittig reaction (**5**→**6**) followed by DDQ oxidation then gave the ketoester **7**, which gave the corresponding hydroxamic acid, trichostatin A (**1**), together with a trace of the Δ^4-stereoisomer. This route has therefore been done in the order *b*, *a*, *c*, *d*, and the overall yield, based on the aldehyde **2**, is 22%.

Route 2. We next sought to simplify the synthesis by carrying out the steps *b* and *c* first to get the ester **8**. We thought that in this way we might avoid the problem posed by our trying to acylate an aldehyde-derived silyl enol ether, and we also hoped to find out whether our observation of γ-acylation of a silyl dienol ether[3] could be extended to ε-acylation of the trienol ether **11** derived from the ester **8**. We easily got the ester **8**, but we were frustrated first by the difficulty we had in preparing the silyl trienol ether **11**. The usual method[14] (LDA, HMPA), which works for sorbate,[15] gave mixtures of compounds. We were more successful, following a suggestion[16] that



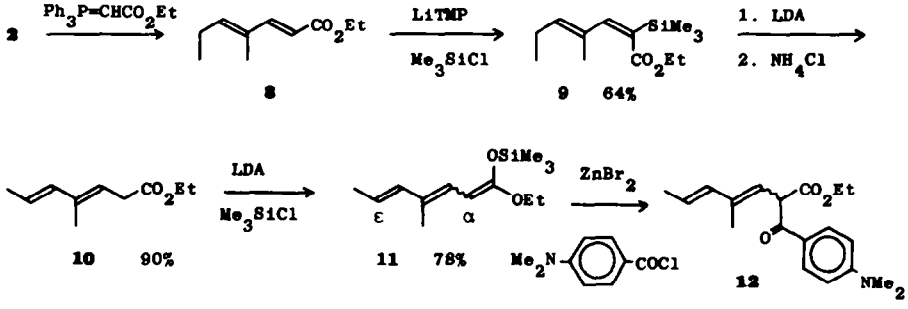
Scheme 1.



Scheme 2.

very hindered bases would avoid conjugate addition when we used lithium tetramethylpiperidide at −100°, but even in this case we were successful only when we added trimethylsilyl chloride *before* adding the base, and the product was not the silyl trienol ether **11** but the C-silyl derivative **9**. It appears that we have here an example of a rather unusual event,[17] the formation of an allenolate. Allenolates derived from ketones are O-silylated,[18] but it is not unreasonable, since ester enolates are more prone than ketone enolates to C-silylation,[19] that an allenolate from an ester should be C-silylated. Presumably the allenolate is very reactive and can only be trapped when the silyl chloride is already in the reaction mixture, an observation which supports our belief that the product **9** is not the result of conjugate addition followed by elimination.[20]

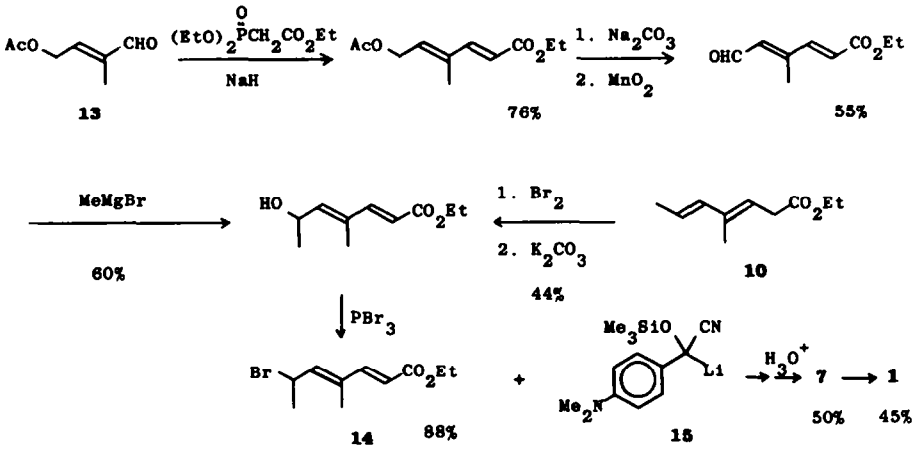
With the enolisable hydrogen now blocked by a silyl group, it was possible to continue: further treatment with lithium tetramethylpiperidide and aqueous work-up now gave the deconjugated ester **10**,[21] and this gave us no



Scheme 3.

trouble in forming the silyl trienol ether **11**. However, our frustrations were compounded when we found that acylation with *p*-dimethylaminobenzoyl chloride took place, most unexpectedly, at the α-position to give the ester **12** as the only isolable product. The yield was low because **12** was rather unstable even to chromatography.

Route 3. We turned next to an alternative and longer established method for encouraging attack at the site remote from the CO group. In this route, we use the umpolung version of Route 2. We prepared the bromoester **14** by the routes shown in Scheme 4. This bromide was a fairly reliable a^6 synthon, and the anion **15** of the silyl-protected[22] cyanohydrin of *p*-dimethylaminobenzaldehyde was a reliable d^1 synthon. They reacted together to give the ester **7**, after a hydrolytic work-up, and this ester gave trichostatin A as before. The overall yield was 4.8% from the aldehyde **13** or 2.8% from the ester **10**.



Scheme 4.

EXPERIMENTAL

4 - t - Butyl - 2 - methyl - 1 - trimethylsilyloxycyclohexene. Chlorotrimethylsilane (15.8 ml, 125 mmol) was added dropwise with stirring to a mixture of 2 - methyl - 4 - t - butylcyclohexanone[23] (20 g, 125 mmol) NaI (18.72 g, 125 mmol) and hexamethyldisilazane (20.17 g, 125 mmol) in n-pentane (150 ml). The mixture was heated at 40° for 8 hr under N_2. After cooling it was filtered and the filtrate washed with sat. $NaHCO_3$ aq, HCl, $NaHCO_3$ aq, and water. The organic layer was dried ($MgSO_4$) and concentrated and the residue distilled using a Vigreux column to give the *silyl enol ethers* as an 88:12 mixture (20.6 g, 86%), b.p. 104–106°/10 mmHg. Chromatography on silica gel gave the major isomer R_f(CH_2Cl_2) 0.85, ν_{max}(film) 1685 and 1250 cm^{-1}, δ ($CDCl_3$) 2.15–1.80 (4H, m), 1.7–1.45 (6H, m), 0.87 (9H, s), and 0.17 (9H, s) (Found: M^+, 240.4617. $C_{14}H_{28}OSi$ requires: M 240.4620).

Ethyl 3 - trimethylsilyloxybut - 2 - enoate. Chlorotrimethylsilane (6.3 ml, 5.43 g, 50 mmol) was added dropwise with stirring to a mixture of ethyl acetoacetate (6.5 g, 50 mmol) and Et_3N (7 ml, 5.05 g, 50 mmol) in THF (100 ml) and the mixture stirred overnight at room temp under N_2. The mixture was filtered, the solvent evaporated *in vacuo*, the residue taken up in ether, washed with $NaHCO_3$ aq, water, dried ($MgSO_4$) and evaporated, and the residue distilled to give the silyl enol ether (8.9 g, 89%) b.p. 101–103°/18 mmHg (lit.[24] b.p. 82–84°/13 mmHg), δ ($CDCl_3$) 4.94 (1H, s), 4.05 (2H, q, *J* 7 Hz), 2.13 (3H, s), 1.06 (3H, t, *J* 7 Hz), and 0.13 (9H, s).

Preparation of other silyl enol ethers. The other silyl enol ethers were prepared by the methods of House *et al.*[25]

2-Benzoylcyclohexanone. Anhyd $ZnBr_2$ (*ca* 25 mg, 0.1 mmol) was added to a soln of benzoyl chloride (2.3 ml, 2.81 g, 20 mmol) and 1-trimethylsilyloxycyclohexene (3.4 g, 20 mmol) in dry CH_2Cl_2 (60 ml) at room temp and the mixture shaken intermittently for 2 hr. Aqueous work-up and chromatography on silica gel gave 2-benzoylcyclohexanone (3.27 g, 81%), m.p. 86–87° (lit.[26] m.p. 87–88°).

2 - Acetyl - 2 - methylcyclohexanone. 2 - Methyl - 1 - trimethylsilyloxycyclohexene (1.84 g, 10 mmol) in CH_2Cl_2 (8 ml) was added dropwise over 15 min with stirring to acetyl chloride (0.78 g, 10 mmol) and titanium tetrachloride (1.09 ml, 1.88 g, 10 mmol) in CH_2Cl_2 (15 ml) at −78°. After 1 hr at −78° the mixture was allowed to come to room temp over 2 hr. It was diluted with ether (20 ml) and added to sat $NaHCO_3$ aq (50 ml). Conventional work-up followed by column chromatography on silica gel gave the β-diketone (1.40 g, 91%) with ^{1}H NMR identical to that reported by Kopka and Rathke.[12]

2 - Acetyl - 6 - methylcyclohexanone. This was prepared similarly, and gave the β-diketone (1.37 g, 89%) with ^{1}H NMR identical to that reported by Kopka and Rathke,[12] except that the signal at δ 1.16 was a 3H doublet (J 7 Hz) and not a singlet. The report of a singlet is clearly a typographical error.

2 - Acetyl - 2 - methyl - 4 - t - butylcyclohexanone. This was prepared similarly, except that the temp was −23° and it was allowed to warm to room temp over 1 hr. The *ca* 1:1 mixture of stereoisomeric *β-diketones* (1.63 g, 78%) had R_f (CH_2Cl_2) 0.55, ν_{max} (film) 1720 and 1710 cm^{-1}, δ ($CDCl_3$) 2.16 and 2.06 (3H, s, COMe's), 1.36 and 1.20 (3H, s, CMe's), 0.91 (9H, s, Bu^t) and a methylene envelope (Found: M^+, 210.3159. $C_{13}H_{22}O_2$ requires: M, 210.3169).

3- Methylhexan - 2,4 - dione. Anhyd $ZnBr_2$ (*ca.* 25 mg, 0.1 mmol) was added to a soln of acetyl chloride (0.78 g, 10 mmol) and 3 - trimethylsilyloxypent - 2 - ene (1.58 g, 10 mmol) in dry CH_2Cl_2 (50 ml) at room temp, and the mixture shaken intermittently. After 2 hr, the mixture was added to sat sodium bicarbonate soln (100 ml), the aqueous layer extracted with CH_2Cl_2 (2 × 20 ml), the combined organic fraction dried ($MgSO_4$), and evaporated *in vacuo*, and the residue chromatographed on silica gel to give the β-diketone (0.98 g, 77%), δ ($CDCl_3$) 3.72 (1H, q, 7 Hz), 2.39 (2H, q, 7 Hz), 2.12 (3H, s), 1.27 (3H, d, 7 Hz), 1.01 (3H, t, 7 Hz), Cu(II) salt m.p. 176–178° (lit.[27] 175–177°).

Ethyl 1-acetylcyclohexanecarboxylate. This was prepared similarly from the silyl enol ether (2.28 g, 10 mmol) and distilled to give the *β-ketoester* (1.32 g, 66%) b.p. 106°/7 mmHg, (Found: C, 66.79; H, 9.39. $C_{11}H_{18}O_3$ requires: C, 66.64; H, 9.15%), δ ($CDCl_3$) 4.2 (2H, q, *J* 7 Hz), 2.15 (3H, s), 2.2–1.3 (10H, m) and 1.30 (3H, t, *J* 7 Hz), *m/z* 198 (1, M^+) and 156 (100, $M^+ - H_2CO$).

Isopentyl 2 - p - (dimethylamino)benzoyl propionate. p-Dimethylaminobenzoic acid (4.66 g) and oxalyl chloride (70 ml) were kept for 2 hr at room temp. The oxalyl chloride was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2 (70 ml). $ZnBr_2$ (140 mg) and the silyl enol ether (6.1 g) were added and the mixture stirred for 30 min. A brine work-up and chromatography

gave the *β-ketoester* (5.56 g, 69%). Bulb to bulb distillation (195°/0.05 mmHg) gave an analytical sample (Found: C 70.06, H, 8.57, N, 4.85. $C_{17}H_{25}NO_3$ requires: (70.07; H, 8.65; N, 4.81%). ν_{max} (KBr) 1749 and 1672 cm^{-1}, δ ($CDCl_3$) 7.85 and 6.60 (4H, AA'BB' system, $J \sim 9$ Hz), 4.30 (1H, q, CHMe J 7 Hz), 4.10 (2H, t, J 6.5 Hz), 3.0 (6H, s), 1.6–1.2 (3H, m), 1.45 (3H, d, J 7 Hz), and 0.95 (6H, d, J 5.5 Hz), m/z 291 (8, M^+) and 148 (100).

Ethyl 3 - acetoxybut - 2 - enoate. This was prepared from the silyl enol ether (2.02 g) by the $ZnBr_2$ method to give the O-acetate (1.39 g, 81%), δ ($CDCl_3$) 5.52 (1H, s) 4.05 (2H, q, J 7 Hz), 2.23 (3H, s), 2.01 (3H, s) and 1.27 (3H, t, J 7 Hz), identical with an authentic sample.[28]

2 - Methylpent - 2 - enol (**2**). 1 - Trimethylsilyloxy - prop - 1 - ene (13 g, 100 mmol) and propionaldehyde (5.8 g, 100 mmol) were added to titanium tetrachloride (11 ml, 18.97 g, 100 mmol) and titanium tetraisopropoxide (5.9 ml, 5.6 g, 20 mmol) in CH_2Cl_2 (50 ml) at −78°, under argon, and stirred for 1 hr at −78°. It was quenched with satd ammonium chloride soln (40 ml), worked up and distilled with I_2 (200 mg) collecting the distillate between 80° and 140°. This was dried ($MgSo_4$) and redistilled to give 2-methylpent-2-enol (3 g, 82%), b.p. 137–139°, (lit.[29] b.p. 134–6°).

2 - Methyl - 1 - trimethylsilyloxypenta - 1,3 - diene (**3**). This was prepared, by the method described for 4 - t - butyl - 2 - methyl - 1 - trimethylsilyloxycyclohexene above, from 2 - methylpent - 2 - enal (9.8 g, 100 mmol) to give **3** (13.26 g, 78%), b.p. 70–72°/16 mmHg lit.[31] 66–69°/15 mmHg, ν_{max} (film) 1608, 1634 and 1260 cm^{-1}, δ ($CDCl_3$) 5.92 (1*H*, s), 5.68 (2*H*, m), 1.98 (3H, d, J 7 Hz) and 1.78 (3H, s) (M^+, 170.3271 $C_9H_{18}OSi$ requires: M, 170.3275).

p-Dimethylaminobenzaldehyde dimethylacetal (**4**). Camphor - 10 - sulphonic acid (*ca.* 50 mg) was added to a soln of *p*-dimethylaminobenzaldehyde (14.9 g, 100 mmol) and trimethylorthoformate (13.25 g, 125 mmol) in MeOH (150 ml). After 2 hr the solvent was evaporated and the residue distilled to give acetal[30] (15 g, 77%), b.p. 153–157°/18 mmHg, ν_{max} (film) 2855 and 1620 cm^{-1}, δ ($CDCl_3$) 7.24 (2H, d, J 9 Hz), 6.62 (2H, d, J 9 Hz), 5.27 (1H, s), 3.28 (6H, s) and 2.91 (6H, s). (M^+, 195.2619. $C_{11}H_{17}O_2N$ requires: M, 195.2619).

(E) - 5 - (4'Dimethylaminophenyl) - 5 - methoxy - 2,4 - dimethyl pent - 2 - enal (**5**). Anhyd $ZnBr_2$ (*ca.* 50 mg, 0.2 mmol) was added to **4** (3.9 g, 20 mmol) and **3** (3.4 g, 20 mmol) in CH_2Cl_2 (125 ml) and the mixture stirred for 5 hr at room temp. Aqueous work-up and chromatography on silica gel gave the *aldehyde* **5** (4.1 g, 79%) R_f (CH_2Cl_2) 0.55, ν_{max} (CH_2Cl_2) 1693, 1619 and 1521 cm^{-1}, δ ($CDCl_3$) 9.26 (1H, s), 7.11 (2H, d, J 9 Hz), 6.72 (2H, d, J 9 Hz), 6.38 (1H, d, J 9 Hz), 3.97 (1H, d, J 6 Hz), 3.18 (3H, s), 2.91 (6H, s), 1.57 (3H, s), 1.61 (1H, m) and 1.08 (3H, d, J 7 Hz). (Found: M^+, 261.3642. $C_{16}H_{23}O_2N$ requires: M, 261.3648).

Ethyl (E,E) - 7 - (4' - dimethylaminophenyl) - 7 - methoxy - 4,6 - dimethylhepta - 1,3 - dienoate (**6**). NaOSt from Na (0.75 g) in EtOH (100 ml) was added to carboethoxymethyl triphenyl-phosphonium bromide (4.15 g, 10 mmol) and **5** (2.61 g, 10 mmol) in EtOH (100 ml) and the mixture kept at room temp for 3 hr. The EtOH was evaporated off *in vacuo*, the residue taken into CH_2Cl_2 (100 ml), washed with water (2 × 30 ml) and dried ($MgSo_4$). The solvent was evaporated *in vacuo* and the residue chromatographed on silica gel to give the *ester* **6** (2.91 g, 88%) as a gum, ν_{max} (CH_2Cl_2) 1707, 1625, 1620 and 1523 cm^{-1}, δ ($CDCl_3$) 6.97 (2H, d, J 9 Hz), 6.67 (2H, d, J 9 Hz), 5.35–5.74 (3H, m), 4.06 (2H, q, J 6 Hz), 3.93 (1H, d, J 6 Hz), 3.13 (3H, s), 2.87 (6H, s), 1.67 (1H, m), 1.56 (3H, s), 1.23 (3H, t, J 6 Hz) and 1.02 (3H, d, J 7 Hz) (Found: M^+, 331.4554, $C_{20}H_{29}O_3N$ requires: M, 331.4560).

Ethyl (E,E) - 6 - (4' - Dimethylaminobenzoyl) - 4 - methyl - 2,4 - heptadienoate (**7**). Dichlorodicyanoquinone (1.36 g, 6 mmol) in benzene (10 ml) was added to **6** (1.65 g, 5 mmol) in benzene (20 ml) and stirred at room temp for 15 min. Aqueous work-up and chromatography on silica gel gave the *ester* **7** (1.38 g, 88%), ν_{max} (CH_2Cl_2), 1712, 1665, 1624, 1595 and 1530 cm^{-1}, δ ($CDCl_3$) 7.82 (2H, d, $J \sim 9$ Hz) and 6.68 (2H, d $J \sim 9$ Hz) 7.30 (1H, d), 6.05 (1H, br d), 5.85 (1H, d, J 15.5 Hz), 4.40 (1H, dq, J 9.5 and 7 Hz), 4.20 (2H, q, J 6 Hz), 3.04 (6H, s), 1.92 (3H, s), 1.29 (3H, d, J 7 Hz), 1.21 (3H, t, J 6 Hz) (Found: C, 72.46; H, 7.93; N, 4.52. $C_{19}H_{25}NO_3$ requires: C, 72.35; H, 7.99; N, 4.44%) (Found: M^+, 315.4131, $C_{19}H_{25}NO_3$ requires: M, 315.4133), m/z 315 (0.8, M^+), 228 (1.5), 148 (100). The stereochemistry of the Δ^4-double bond was proved by an 11.5% nOe from H-5 to H-3.

Trichostatin A (**1**). Hydroxylamine hydrochloride (3.2 g, 46 mmol) in MeOH (8 ml) was mixed at 40° with KOH (2.58 g, 46 mmol) in MeOH (5 ml), cooled to 0° and filtered. The ester **7** (1.57 g, 5 mmol) was then added to the filtrate followed by KOH (0.49 g, 8.7 mmol) at room temp over a period of 0.5 hr with vigorous stirring. After 4 hr, water (30 ml) was added, followed by 0.1 N HCl until pH reached 6.5. The ppt was filtered off and kept overnight with MeOH (10 ml) to give (±)-trichostatin A (0.69 g, 46%), m.p. 180–182°, lit.[4] (optically active) 150–151° (Found: C, 67.23; H, 7.36; N, 9.14. $C_{17}H_{23}N_2O_3$ requires: C, 67.53, H, 7.33; N, 9.26%). The ^1H NMR spectrum was identical to that of an authentic sample.

Ethyl (E,E) - 4 - methyl - 2 - (trimethylsilyl)hepta - 2,4 - dienoate (**9**). BuLi (81 ml of a 2.2 M soln in hexane) was added to 2,2,6,6,-tetramethylpiperidine (25.42 g, 0.18 mmol) in THF (200 ml) at −15° and after 15 min the mixture was cooled to −100°. Chlorotrimethylsilane (38.8 g, 0.36 mmol) was added followed by **8**[32] dropwise over 30 min. After 1 hr the solvent was evaporated off, the residue taken up in hexane, filtered, concentrated and distilled twice to give the *ester* **9** (23.06 g, 64%) b.p. 56°/0.08 mm (97.6% pure by GC) (Found: C, 64.97; H, 10.17. $C_{13}H_{24}O_2Si$ requires: C, 64.95; H, 10.06%), δ ($CDCl_3$) 6.30 (1H, s), 5.65 (1H, t, J 7.5 Hz), 4.2 (2H, q, J 7 Hz, 2.15 (2H, dq, J 7.5 and 7.5 Hz), 1.75 (3H, br s), 1.30 (3H, t, J 7 Hz), 0.95 (3H, t, J 7.5 Hz) and 0.15 (9H, s); m/z 240 (10, M^+) and 211 (100). The stereochemistry was determined by 7% nOe from Me_3Si to H-3, 20% nOe from H-3 to H-5 and 17% nOe from H-5 to H-3.

Ethyl (E,E) - 4 - methylhepta - 3,5 - dienoate (**10**). BuLi (182 ml of a 1.6 M soln in hexane) was added to diisopropylamine (32.75 g, 0.32 mol) in THF (500 ml) at −20° and then cooled to −78° and hexamethylphosphoric triamide (70 ml, 0.4 mol) added, followed after 30 min by **9** (57.93 g, 0.24 mol). The mixture was allowed to come to 0° and sat NH_4Cl aq (150 ml) was added. Aqueous work up and distillation gave the *ester* **10** (36.4 g, 90%) b.p. 57°/0.5 mmHg (97% pure by GC) (Found: C, 71.21; H, 9.64. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59) ν_{max} 1745 cm^{-1}, δ ($CDCl_3$) 6.10 (1H, d, J 16 Hz), 5.65 (1H, dq, J 16 and 6.5 Hz), 5.5 (1H, t, J 7.5 Hz), 4.15 (2H, q, J 7 Hz), 3.15 (2H, d, J 7.5 Hz), 1.75 (3H, d, J 6.5 Hz), 1.70 (3H, s) and 1.3 (3H, t, J 7 Hz) m m/z 168 (15, M^+) and 95 (100). The stereochemistry was determined by the ^{13}C resonance for the C-4 Me group at 12.72 ppm. A Me group in the corresponding *Z*-compound is expected at ~ 21 ppm.[33]

1 - Ethoxy - 4 - methyl - 1 - (trimethylsilyloxy)hepta - 1,3,5 - triene (**11**). n-BuLi (2.3 ml of a 2.1 M soln in hexane) was added to diisopropylamine (606 mg, 6 mmol) in THF (10 ml) at −20° and cooled to −78° after 30 min. The ester **10** (666 mg, 4 mmol) and chlorotrimethylsilane (1.2 g, 10.7 mmol) were added and the temp allowed to rise to 0°. The solvent was evaporated off, the residue taken up in hexane, filtered, concentrated, and distilled bulb to bulb (160°/0.2 mm) to give **11** (748 mg, 78%) which was a 1:1 mixture of stereoisomers δ ($CDCl_3$) 6.15 (1H, d, J 15 Hz), 6.10 (1H, d, J 11 Hz), 5.45 (1H, dq, J 15 and 7 Hz), 4.7 and 4.5 (1H, 2d, J 11 Hz), 3.9 and 3.8 (2H, 2q, J 7 Hz), 1.75 (3H, d, J 7 Hz), 1.70 (3H, s), 1.30 and 1.25 3.8 (2H, 2q, J 7 Hz), and 0.25 and 0.20 (9H, 2s).

Ethyl 2 - p - (dimethylamino)benzoyl - 4 - methylhepta - 3,5 - dienoate (**12**). *p*-Dimethylaminobenzoic acid (285 mg, 1.55 mmol) was converted to the acid chloride, as described and dissolved in CH_2Cl_2 (3 ml). $ZnBr_2$ (30 mg) was added and then, at 0°, **11** (335 mg, 1.4 mmol) in dichloromethane (1 ml). After 10 min the mixture was added to 2N $NaHCO_3$ aq (20 ml). Aqueous work-up gave crude product (350 mg) and flash chromatography eluting with toluene–ether (95:5) gave the pure unstable **12**, δ ($CDCl_3$) 7.8 and 6.6 (4H, AA'BB' system, $J \sim 9$ Hz), 6.10 (1H, br d, J 15.5 Hz), 5.75 (1H, br d), 5.6 (1H, dq, J 15.5 and 6.5 Hz), 5.10 (1H, d, J 9.5 Hz), 4.10 (2H, q, J 7 Hz), 3.0 (6H, s), 1.80 (3H, d, J 1 Hz), 1.7 (3H, d, J 6.5 Hz) and 1.20 (3H, *d*, J 7 Hz).

Ethyl (E,E) - 6 - acetoxy - 4 - methylhexa - 2,4 - dienoate. Triethyl phosphoroacetate (43.23 g, 0.19 mol) was added to NaH (4.63 g, 0.19 mol) in THF (100 ml) at 0–5°, followed

by **13**[34] (25 g, 0.18 mol) in THF (50 ml). After 20 hr at room temp, EtOAc (200 ml) was added, and a brine work-up and distillation gave the *ester* (28.6 g, 76%) b.p. 103°/0.35 mm (Found: C, 61.87; H, 7.53. $C_{11}H_{16}O_4$ requires: C, 62.25; H, 7.60%), ν_{max} 1740, 1717 and 1623 cm^{-1}, δ ($CDCl_3$) 7.30 (1H, d, *J* 15.5 Hz), 5.95 (1H, d, *J* 15.5 Hz), 5.95 (1H, br t, *J* 6.5 Hz), 4.80 (2H, br d, *J* 6.5 Hz), 4.25 (2H, q, *J* 7 Hz), 2.10 (3H, s), 1.85 (3H, d, *J* 1 Hz) and 1.30 (3H, t, *J* 7 Hz), *m/z* 212 (9, M^+), 197 (7) and 139 (100). The stereochemistry of the Δ^4-double bond was not proved but assumed to be *E*, as in the starting material.

Ethyl (E,E) - 6 - *hydroxy* - 4 - *methylhexa* - 2,4 - *dienoate*. The acetoxy ester (27.54 g, 0.13 mol) Na_2CO_3 (20 g) and triethanolamine (2 ml) were refluxed in EtOH (250 ml) for 3 hr. EtOAc and brine were used in the work up to give the *alcohol* (15.66 g, 71%) b.p. 110°/0.4 mm (Found: C, 63.31; H, 7.98. $C_9H_{14}O_3$ requires: C, 63.51; H, 8.29%), ν_{max} 3425, 1711 and 1522 cm^{-1}, δ ($CDCl_3$) 7.30 (1H, d, *J* 16 Hz), 6.0 (1H, br t, *J* 7 Hz), 5.90 (1H, d, *J* 16 Hz), 4.35 (2H, d, *J* 7 Hz), 4.20 (2H, q, *J* 7 Hz), 2.5 (1H, OH), 1.80 (3H, d, *J* 1 Hz) and 1.30 (3H, t, *J* 7 Hz), *m/z* 170 (6, M^-), 152 (10), 141 (21) and 43 (100).

Ethyl (E,E) - 6 - *oxo* - 4 - *methylhexa* - 2,4 - *dienoate*. The alcohol (11.68 g) and MnO_2 (30 g) were stirred at room temp for 4 hr in CH_2Cl_2 (200 ml). The mixture was filtered, the solvent evaporated and the residue crystallised from hexane cyclohexane to give the *aldehyde* (9.04 g, 78%), m.p. 48–49° (Found: C, 64.19; H, 7.26. $C_9H_{12}O_3$ requires: C, 64.27; H, 7.19%), ν_{max} (KBr) 1719, 1668, 1636 and 1593 cm^{-1}, δ ($CDCl_3$) 10.20 (1H, d, 7.5 Hz), 7.45 and 6.35 (2H, AB system, *J* 15.5 Hz), 6.70 (1H, br d, *J* 7.5 Hz), 4.30 (2H, q, *J* 7 Hz), 2.30 (3H, d, *J* 1.5 Hz) and 1.35 (3H, t, *J* 7 Hz), *m/z* 168 (15, M^+), 139 (21), 123 (32) and 95 (100).

Ethyl(E,E) - 6 - *hydroxy* - 4 - *methylhepta* - 2,4 - *dienoate*. MeMgBr (130 ml of a 0.39 M soln in ether) was added to the aldehyde (8.0 g, 47.6 mmol) in ether (200 ml) over 30 min at 20–28°. NH_2Cl aq work-up and flash chromatography eluting with hexane/EtOAc (7:3) gave the *alcohol* (5.24 g, 60%) (Found: C, 65.44; H, 8.83. $C_{10}H_{16}O_3$ requires: C, 65.19; H, 8.75%), ν_{max} 3426, 1713 and 1623 cm^{-1}, δ ($CDCl_3$) 7.25 and 5.90 (2H, AB system, *J* 15.5 Hz), 5.85 (1H, br d, 8.5 Hz), 4.70 (1H, dq, *J* 8.5 and 6 Hz), 4.2 (2H, q, *J* 7 Hz), 2.3 (1H, s, OH), 1.85 (3H, d, *J* 1.5 Hz), 1.32 (3H, d, *J* 6 Hz) and 1.30 (3H, t, *J* 7 Hz), *m/z* 184 (0.2, M^+), 141 (50), 138 (35) and 95 (100). The stereochemistry of the Δ^4-double bond was confirmed as *E* by a 22% nOe from the vinyl methyl signal to H-2 and 15% to H-6. The same alcohol was got from 10 (2.65 g) in CCl_4 (20 ml) added to Br_2 (2.52 g) in CCl_4 (5 ml) at 0°. The solvent was evaporated, the residue dissolved in dimethyl formamide (60 ml) and stirred vigorously with K_2CO_3 (8 g) for 18 hr at room temp and 2 hr at 80°. Aqueous work-up using EtOAc, and flash chromatography gave the same ester (1.28 g, 45%).

Ethyl 6 - *bromo* - 4 - *methylhepta* - 2,4 - *dienoate* (**14**). PBr_3 (5.46 g, 20.17 mmol) in hexane (5 ml) was added slowly at 0° to the alcohol (7.43 g, 40.34 mmol) in ether (50 ml) and the mixture stirred at room temp for 1 hr. Aqueous work-up gave an oil (8.74 g, 88%) which was used without purification, δ 7.3 and 6.0 (2H, AB system, *J* 15.5 Hz), 6.05 (1H, *d*, *J* 10.5 Hz), 5.05 (1H, dq, *J* 10.5 and 6 Hz), 4.25 (2H, *q*, *J* 7 Hz), 1.85 (3H, s), 1.80 (3H, d, *J* 6 Hz) and 1.30 (3H, t, *J* 7 Hz).

Ethyl (E,E) - 6 - *p*(*dimethylamino*)*benzoyl* - 4 - *methylhepta* - 2,4 - *dienoate* (7). n-BuLi (25.3 ml of a 1.6 M soln in hexane) was added to diisopropylamine (4.09 g) in THF (35 ml) at −10°. After 30 min the mixture was cooled to −70°, the cyanohydrin silyl ether[22] of dimethylaminobenzaldehyde (8.36 g, 33.7 mmol) in THF (5 ml) was added over 30 min, followed by **14** (8.74 g, 35.7 mmol) in THF (5 ml), and the mixture kept for 2 hr INHCl (80 ml) and EtOAc (100 ml) were added and the mixture stirred for 18 hr at room temp. The organic layer was shaken with 1N NAOH aq (100 ml), concentrated and flash chromatographed eluting with toluene/EtOAc (95:5) to give **7** (5.28 g, 50%) as an oil identical with the sample described above.

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