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Preparation of the Three C1-C7, C8-C15 and C16-N22 Fragments of the Hsp90 Inhibitor Herbimycin A.

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Abstract:

The construction of the three C16-N22 **2**, C1-C7 **23** and C8-C15 **32** segments of the Hsp90 inhibitor herbimycin A **1** is reported. 1-Iodo-3-nitro-2,5-diphenol compound **2** was obtained in 55% yield for 3 steps from the commercially available diiodo derivative **7**. Reaction between 1,1-dibromo-alkene **22** and vinyltin **17a** using Pd(PPh₃)₄ or Pd(CH₃CN)₂Cl₂/CuI/diisopropylethylamine, in toluene or DMF at 85°C, led to enyne **23** in 63% yield (19% overall yield from isopropylidene glyceraldehyde). The synthesis of the C8-C15 sub-unit **32** was performed in 13 steps in 3.4% overall yield from the commercially available ester **24**, with a Hoppe crotylation as a key step.

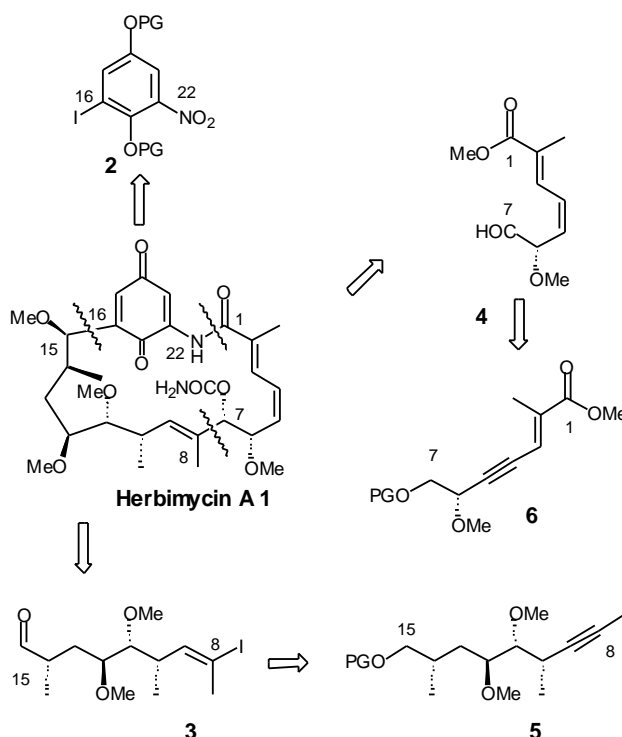
Molecular chaperones such as heat shock protein 90 (HSP90) assist the folding, maturation and subcellular localisation of their client proteins, and target damaged proteins for degradation via the proteasome. Therefore, the inhibition of Hsp90 provides a novel approach toward regulating crucial enzymes involved in the progression of cancer. The benzoquinoid ansamycins, such as herbimycin A and geldanamycin, have recently been identified as inhibitors of the Hsp90 folding process. Consequently, these molecules are getting a lot of attention in the literature.¹

Herbimycin A **1**² was isolated from the fermentation broth of *Streptomyces hygroscopicus* strain AM-3672, and exhibits pronounced antitumor and antiangiogenic properties. At this time, only two syntheses of herbimycin A **1** has been reported.³

Our synthetic plan developed for herbimycin A **1** involves the convergent approach depicted in Scheme 1. Our intention was to employ metal-catalysed coupling reactions to form both the C15-C16

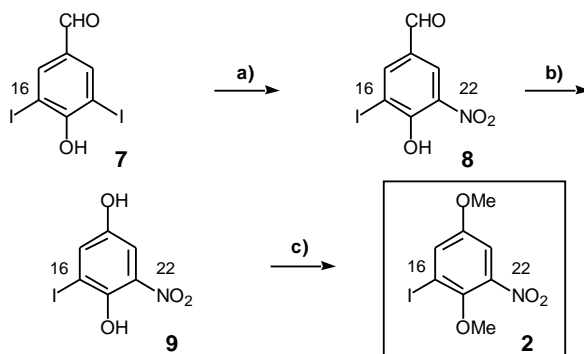
bond between the Northern C16-N22 aromatic fragment **2** and the Southern C8-C15 side chain **3**, and the C7-C8 link between the Eastern C1-C7 dienyl sub-unit **4** and segment **3**. A macrolactamization was programmed for the final cyclization step at N22-C1.

The present work describes the preparation of C16-N22 diphenol **2**, C1-C7 enyne **6** and C8-C15 alcohol **5** (as precursors of compounds **4** and **3**, respectively).



Scheme 1

Northern fragment **2** preparation was effected in 3 steps in 55% overall yield from the commercially available diiodo compound **7**. Mono-nitration of **7** under classical conditions led to nitro-aldehyde **8** in 80% yield. In order to generate the diphenol derivative **9**, we took advantage of the aldehyde function to perform a Baeyer-Villiger oxidation. This reaction cleanly delivered compound **9** in 80% yields.

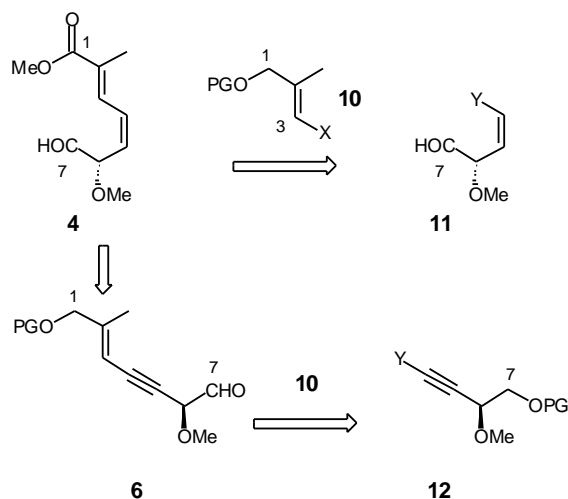


a) NaNO_2 (1 equiv.), AcOH 80°C, 15 h, **80%**. **b)** *m*-CPBA (3 equiv.), CH_2Cl_2 4°C, 15 h, **80%**. **c)** KOH, CH_3I , DMF, 20°C, 4 h, **85%**.

Scheme 2

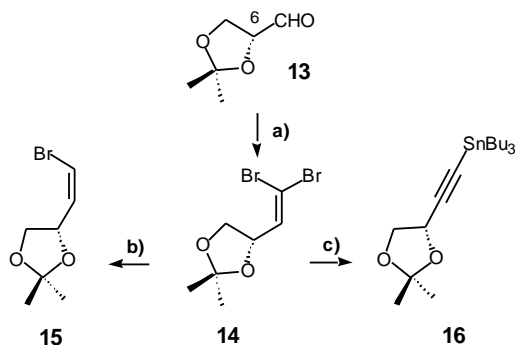
The last step for the preparation of C16-N22 Northern fragment **2** was achieved by methylation of **9** with KOH/CH₃I in DMF at 20°C for 4 h, in 85% yield.⁴

For the Eastern fragment **4** synthesis, a Stille Pd(0)-catalysed coupling reaction was planned between vinyl partners **10** and **11** (Scheme 3), or between **10** and acetylenic compound **12**. In this approach, a partial reduction of the resulting enyne **6** is required to reach the desired compound **4**.



Scheme 3

For synthesis of **11** and **12**, isopropylidene glyceraldehyde **13**⁵ was elected as an appropriate starting material to introduce the C-6 centre (Scheme 4). Application of the Corey-Fuchs method⁶ then led to dibromo alkene **14**, which is a versatile intermediate.⁷

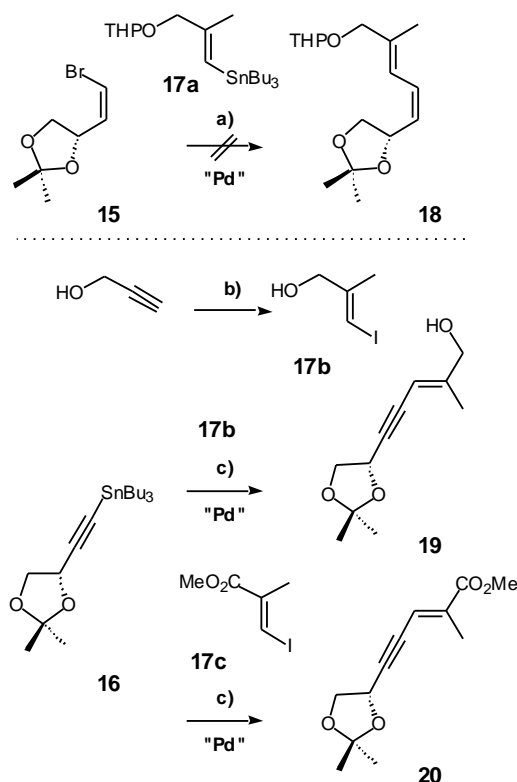


a) Zn (3 equiv.), CBr₄ (3 equiv.), PPh₃ (3 equiv.), CH₂Cl₂, 20°C 12 h, **65%**. b) Bu₃SnH (1.1 equiv.), Pd(PPh₃)₄, THF, 20°C 20 min **90%**. c) *n*-BuLi (3 equiv.), -40°C 2 h, Bu₃SnCl, 20°C, 1 h, **95%**.

Scheme 4

1,1-Dibromo-1-alkene **14** delivered pure (*Z*)-vinyl bromide **15** under Bu₃SnH/Pd(0) conditions, in 90% yield (Scheme 5).⁸ Besides, acetylenic compounds **16**⁷ (95% yield) was easily obtained by *n*-BuLi treatment of **20**, followed by Bu₃SnCl trap.

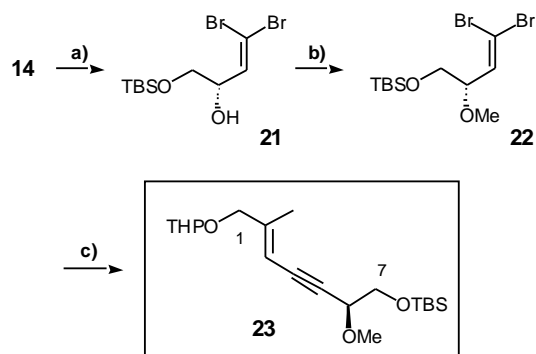
However, we were disappointed to find out that Stille coupling reaction of vinylbromide **15** and vinyltin **17a**⁹ did not lead to the expected coupling product **18**, even with Pd(PPh₃)₄ or Pd(CH₃CN)₂Cl₂, in THF, toluene or DMF, and with CuI or CuCN additives (Scheme 5). Furthermore, tributylstannylalkyne **16** and vinyliodide **17b** or **17c**¹⁰ were coupled using [PdCl(PPh₃)₂Bn (15 mol%) and CuI (30 mol%), in toluene at 85°C, in a modest 30% yield to deliver enynes **19** or **20**.¹¹ These results showed that (*Z*) or trisubstituted olefins **15**, **17a**, **17b** and **17c** did not undergo efficient Stille coupling reactions.¹²



a) Pd(PPh₃)₄ or Pd(CH₃CN)₂Cl₂ (15 mol%), CuI (30 mol%), THF, toluene or DMF, 85°C. **b)** Cp₂ZrCl₂ (0.25 equiv.), AlMe₃ (3 equiv.), CH₂Cl₂, 20°C 24 h, then I₂ (1.2 equiv.), 0°C, **25%**. **c)** **17b** or **17c**, PdCl(CH₃CN)₂Bn (15 mol%), CuI (30 mol%), toluene, 85°C, 12 h, **30%**.

Scheme 5

Consequently, we turned to the Shen method.¹³ Compound **14** was first transformed in 3 steps *via* alcohol **21** into the corresponding 1,1-dibromo-alkene derivative **22** in 45% overall yield (Scheme 6).¹⁴ Compounds **22** and **17a** under Shen's conditions [Pd(PPh₃)₄ or Pd(CH₃CN)₂Cl₂/CuI/diisopropylethylamine, in toluene or DMF at 85°C] conducted to the expected enyne **23** in 63% yield.¹⁵

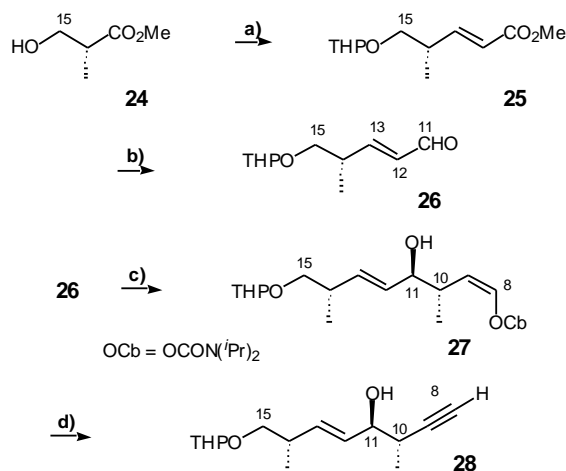


a) i- Amberlyst 15, MeOH, 20°C, 12 h, **71%**. **ii-** TBSCl, Im, CH₂Cl₂ 20°C, 10 h, **91%**. **b)** MeI (excess), THF/DMF 8:1, NaH (1.3 equiv.), 0°C, 3 h, **70%**. **c)** **17a**, Pd(CH₃CN)₂Cl₂ (15 mol%), CuI (30 mol%), DIPEA (1.5 equiv.), DMF, 85°C, 12 h, **63%**.

Scheme 6

In summary, preparation of the Eastern part **23**, precursor of the dienyl fragment **4** of herbimycin A **1**, was achieved in 19% overall yield for 5 steps from the known glyceraldehyde derivative **13**.

The elaboration of Southern C8-C15 sub-unit **5** started from the commercially available hydroxy-ester **24**; classical transformations gave access, *via* ester **25**, to the α,β -unsaturated aldehyde **26** in 50% overall yield for 6 steps (Scheme 7).



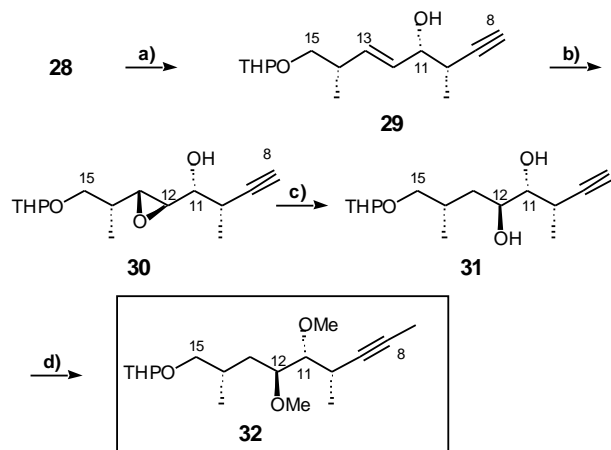
a) i- DHP, APTS, 20°, 12 h, **95%**. **ii-** LAH (0.8 equiv.)/THF, 0°C, 3 h, **85%**. **iii-** IBX (2.2 equiv.), DMSO, 20°C, 2 h, **quantitative**. **iv-** (C₆H₅)₃P=CHCO₂Me/toluene, 50°C, 10 h, **81%**. **b) i-** DIBAL-H (2.1 equiv.)/THF, -78°C, 1 h, **80%**. **ii-** IBX (2.2 equiv.), DMSO, 20°C 2 h, **95%**. **c)** (*E*)-crotyl (diisopropyl)carbamate (2.6 equiv.), 1.6M *n*-BuLi in hexane (2.4 equiv.), (-)-sparteine (2.3 equiv.), -78°C 10 min, then -78°C 3 h for crystallisation. Then Ti(*O*^{*i*}Pr)₄ (6 equiv.), pentane, -50°C and -78°C, 30 min for transmetalation, **26** -78°C, 2 h, **85%**. **d)** *tert*-BuLi (3.1 equiv.)/Et₂O, -78°C, 45 min, **70%**.

Scheme 7

Elaboration of the C15-C8 skeleton was initiated by an enantioselective Hoppe crotylation¹⁶ of aldehyde **26** to afford the pure

vinyl carbamate **27** in 85% yield (100%de) (Scheme 7). Further *tert*-BuLi (3 equiv.) treatment of **27** then delivered the expected acetylenic derivative **28** in 70% yield.

Since it results from a Hoppe aldehyde allylation reaction, compound **28** exhibits an *anti* relationship between the methyl group at C10 and the OH function at C11; therefore, an inversion of the C11 centre was envisaged under the Mitsunobu conditions.



a)- i- DIAD (1.2 equiv.), PPh₃ (1.2 equiv.), PhCO₂H (1.2 equiv.) toluene, -78°C, 10 min, **40%**. **ii-** LiAlH₄ THF, 20°C **80%**. **b)** D-(-)-diethyltartrate (1.2 equiv.), Ti(O^{*i*}Pr)₄ (1.2 equiv.), TBHP (2 equiv.), CH₂Cl₂, -25°C 15 h, **85%**. **c)** DIBAL-H (2.1 equiv.), THF, 0°C 5 h, **60%**. **d)** *n*-BuLi (3.2 equiv.), MeI excess, THF, -78°C -> 20°C 12 h, **70%**.

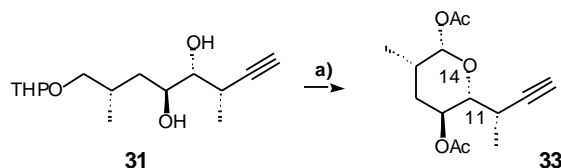
Scheme 8

The C11 hydroxyl function is both in an allylic and a homopropargylic position; as a consequence, application of the Mitsunobu reaction to **28** conducted to the inverted benzoyl ester in a fair 40% yield when the temperature was kept at -78°C for 10 min. Generation of alcohol **29** was then obtained by LiAlH₄ reduction (80% yield, Scheme 8).

At this stage, installation of the secondary C12 alcohol function was envisaged in a two steps sequence. Stereoselective matched Sharpless epoxidation¹⁷ of **29** using D-(-)-diethyltartrate gave epoxide **30** in 85% yield as a pure isomer (the corresponding diastereomer was not observed). Reduction of **30** under DIBAL-H/THF conditions¹⁸ the furnished the *anti*-1,2-diol **31** in 60% yield (the corresponding *anti*-1,3-diol was isolated in 9% yield).

Subsequent methylation of **31** was then carried out using 3.2 equivalents of *n*-BuLi and an excess of MeI to furnish dimethoxy derivative **32** in 70% yield.¹⁹

In this sequence, and in spite of a modest yield for the Mitsunobu reaction, preparation of Southern fragment **32** was achieved in 10% overall yield for 11 steps from the commercially available ester **24**.²⁰ Structural proof for **31** was obtained by NMR analysis of lactol **33**, prepared in a three-step sequence (Scheme 9).



a) i- Amberlyst 15, MeOH 25°C 15 h. **ii-** IBX (2.2 equiv.), DMSO 0°C 1.5 h. **iii-** Ac₂O, pyridine, **63%** yield for 3 steps.

Scheme 9

In conclusion, preparation of Northern fragment **2** of herbimycin A **1** was achieved in 55% yield for 3 steps. Synthesis of the Eastern part **23**, precursor of dienyl fragment **4**, was performed in 19% overall yield for 5 steps from the known glyceraldehyde derivative **13**. Finally, elaboration of the C8-C15 chain **32**, precursor of aldehyde **3**, was accomplished in 3.4% overall yield for 13 steps.

The final synthesis of the Hsp90 inhibitor, herbimycin A **1**, is under study in our laboratory.

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 - 4) **2**: ¹H NMR (270 MHz, CDCl₃) δ 7.60 (d, *J* = 2.5 Hz, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H, CH₃, OMe), 3.60 (s, 3H, CH₃, OMe). MS (GC, EI), *m/z* 309 (M⁺).
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 - 11) **19**: ¹H NMR (270 MHz, CDCl₃) δ 5.54 (s wide, 1H), 4.82 (dd, *J* = 6.4, 6.2 Hz, 1H), 4.11 (dd, *J* = 7.8, 6.2 Hz, 1H), 4.04 (s, 2H), 3.86 (dd, *J* = 7.8, 6.4 Hz, 1H), 1.81 (s, 3H, CH₃), 1.57 (s, 1H, OH), 1.43 (s, 3H, CH₃), 1.33 (s, 3H, CH₃).
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 - 14) **22**: ¹H NMR (270 MHz, CDCl₃) δ 6.29 (d, *J* = 8.0 Hz, 1H), 3.93 (m, 1H), 3.63 (m, 2H), 3.29 (s, 3H, CH₃, OCH₃), 0.82 [s, 9H, 3CH₃, SiC(CH₃)₃], 0.01 [s, 6H, 2CH₃, Si(CH₃)₂].
¹³C NMR (67.8 MHz, CDCl₃) δ 137.2 (CH), 92.4 (C), 82.2 (CH), 64.4 (CH₂), 57.2 (CH₃, OCH₃), 25.8 [3CH₃, SiC(CH₃)₃],

18.3 [C, SiC(CH₃)₃], -4.0, - 4.5 [2CH₃, Si(CH₃)₂].

MS (CI, NH₃), *m/z* 392 (MH⁺ + NH₃), 375 (MH⁺).

- 15) **23**: ¹H NMR (400 MHz, CDCl₃) δ 5.61 (broad s, 1H), 4.61 (t, *J* = 3.3 Hz, 1H), 4.19 (d, *J* = 14.4 Hz, 1H), 4.17 (m, 1H), 3.94 (d, *J* = 14.4 Hz, 1H), 3.84 (m, 1H), 3.79 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.77 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.51 (m, 1H), 3.45 (s, 3H, CH₃, OCH₃), 1.89 (s, 3H, CH₃), 1.73-1.58 (m, 6H, 3CH₂), 0.82 [s, 9H, 3CH₃, SiC(CH₃)₃], 0.01 [s, 6H, 2CH₃, Si(CH₃)₂].

¹³C NMR (67.8 MHz, CDCl₃) δ 148.5 (C), 105.5 (CH), 98.1 (CH), 90.0 (C), 84.2 (C), 73.9 (CH), 70.6 (CH₂), 66.7 (CH₂), 62.5 (CH₂), 57.3 (CH₃, OCH₃), 30.9 (CH₂), 26.4 [3CH₃, SiC(CH₃)₃], 25.8 (CH₂), 19.7 (CH₂), 18.9 [C, SiC(CH₃)₃], -4.8 -4-7 [2 CH₃, Si(CH₃)₂]

MS (CI, NH₃), *m/z* 386 (MH⁺ + NH₃), 369 (MH⁺).

IR (CCl₄) 2929, 2856, 2360, 2341, 1578, 1463, 1129, 869 cm⁻¹.

Anal. Calcd for C₂₀H₃₆O₄Si, 368.58, C 65.17%, H 9.84%.

Found C 65.35%, H, 9.97%.

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- 19) **32**: ¹H NMR (270 MHz, CDCl₃) δ (*two diastereomers*) 4.55 (m, 1H), 3.80 (m, 1H), 3.65 (m, 1H), 3.50 (m, 1H), 3.39, 3.37 (2s, 3H, CH₃, CH₃O), 3.28, 3.26 (2s, 3H, CH₃, CH₃O), 3.20 (m, 1H), 3.03 (m, 1H), 3.24 (m, 1H), 2.79 (m, 1H), 2.03 (m, 1H), 1.78 (s, 3H, CH₃), 1.73-1.58 (m, 6H, 3CH₂), 1.68 (m, 1H), 1.42, (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H, CH₃), 0.99 (d, *J* = 6.9 Hz, 3H, CH₃). ¹³C NMR (67.5 MHz, CDCl₃) δ (*two diastereomers*) 98.7, 98.5 (CH), 81.4 (CH), 80.5 (CH), 80.1 (CH), 79.0 (C), 72.4, 72.3 (CH₂), 62.4 (C), 61.5, 61.2 (CH₃, CH₃O), 57.9, 57.8 (CH₃, CH₃O), 33.1 (CH₂), 30.4, 30.2 (CH₂), 29.2 (CH), 28.8

(CH), 25.4, 25.3 (CH₂), 19.3, 19.2 (CH₂), 18.3 (CH₃), 17.8 (CH₃), 3.5 (CH₃). **Anal.** Calcd for C₁₈H₃₂O₄, 312.44; C, 69.19; H, 10.32. Found C, 69.03; H, 10.56.

- 20) A second approach was also explored from the same starting material **24**. This route used more conventional transformation to reach the desired fragment in a 6% overall yield for 17 steps, with a Sharpless dihydroxylation and a Brown crotylation to introduce the stereogenic centres.

