Highly stereocontrolled total synthesis of (+)-bengamide E

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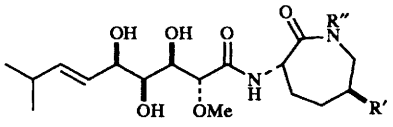
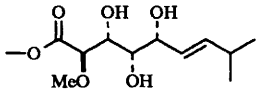
Diisopropyl D-tartrate **7** was efficiently transformed into the hexacarbonyl dicobalt complexed aldehyde **23**. A highly stereocontrolled aldol reaction of **23** with the *O,S*-acetal **20** in the presence of tin(IV) chloride provided, after decomplexation, the aldol adduct **21** as the sole product, which was subsequently converted into (+)-bengamide E **5**.

Bengamides A–F (**1**–**6**),[1] isolated from a Choristid sponge from the Fiji Islands, have been found to possess the (2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-trihydroxy-2-methoxy-8-methylnon-6-



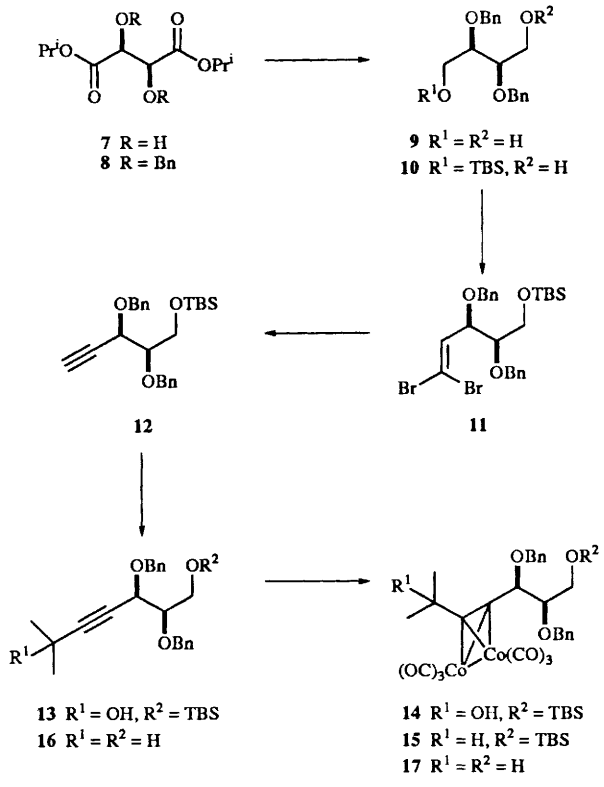
	R′	R″
Bengamide A **1**	$OCO(CH_2)_{12}CH_3$	H
B **2**		Me
C **3**		H
D **4**		Me
E **5**	H	H
F **6**		Me

enyl framework (C-10 side chain) as a common structural feature. Some of them (bengamides A and B) showed significant antihelminthic activity as well as cytotoxicity. Much effort has so far been directed towards the stereoselective construction of the C-10 side chain in order to develop a general procedure for the total synthesis of the bengamide family. Since the first report on the total synthesis of bengamide E by Chida *et al.*[2a] in 1991, several groups have reported total syntheses of bengamides E,[2] B,[2b,3] A[4] and the C-10 side chain,[5] starting from natural sources such as cyclitol,[2a,3,4] glucose,[2b,c,5] tartaric acid[2d] and glyceraldehyde.[2e]

In addition to these syntheses, we have recently completed a highly stereoselective total synthesis[6] of bengamide E **5** on the basis of the newly developed *syn*-selective aldol reaction of the cobalt-complexed propynal with the *O*-silyl ketene *O,S*-acetal. This method, however, suffered from the optical resolution of diastereoselectively obtained racemic *syn*-aldol products. In this paper we describe another highly stereocontrolled total synthesis of (+)-bengamide E5 by taking advantage of the two chiral centres of D-tartaric acid.

Results and discussion

At the outset, commercially available diisopropyl D-tartrate **7** was treated with benzyl bromide and tetrabutylammonium iodide in the presence of 18-crown-6[7] to give the dibenzyl derivative **8** in 80% yield. Exposure of **8** to lithium aluminium hydride (LAH) afforded the diol **9** (88%), which was subsequently mono-protected by treatment with one equivalent of sodium hydride (NaH) and *tert*-butyldimethylsilyl (TBS) chloride in THF to provide the mono-silylated product **10** in 90% yield. Swern oxidation of **10**, followed by Corey and Fuchs' dibromoolefination[8] with triphenylphosphine and carbon tetrabromide produced the olefin **11** in 65% yield. Transformation of the dibromoolefin moiety into a triple bond[8] was realised by treatment of **11** with butyllithium (BuLi) in diethyl ether at 0 °C to give the acetylene derivative **12** in 96% (Scheme 1).



7 R = H
8 R = Bn

9 $R^1 = R^2 = H$
10 R^1 = TBS, R^2 = H

12

11

13 R^1 = OH, R^2 = TBS
16 $R^1 = R^2 = H$

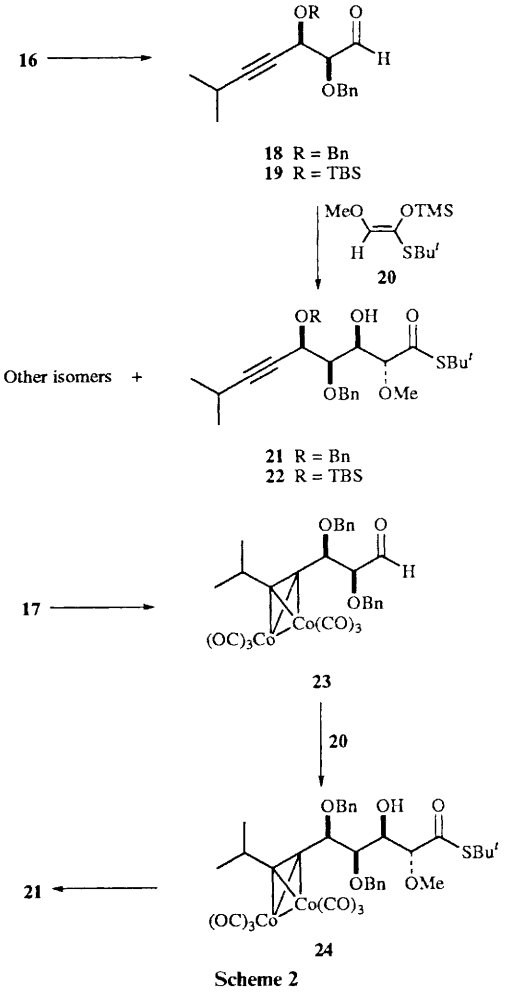
14 R^1 = OH, R^2 = TBS
15 R^1 = H, R^2 = TBS
17 $R^1 = R^2 = H$

Scheme 1

The next step required for our synthesis was the introduction of an isopropyl group at the triple bond terminus of **12**. Unfortunately several attempts at the direct conversion of **11** into **13** by successive treatment with BuLi and acetone resulted in the production of a mixture of **12** and **13** together with the starting **11**. Therefore, a stepwise procedure was found to be better in this case. The acetylide anion of **12** was generated with BuLi in THF at −78 °C and subsequently trapped with acetone to furnish **13** in 84% yield. Reductive deoxygenation of **13** according to Lau's report[9] was examined. The hydroxy compound **13** was treated with sodium cyanoboranuide ($NaBH_3CN$) in methylene chloride in the presence of zinc iodide at reflux, however, no reaction took place and **13** remained intact. We noticed at this stage that hexacarbonyldicobalt complexation of the triple bond in **13** would facilitate the

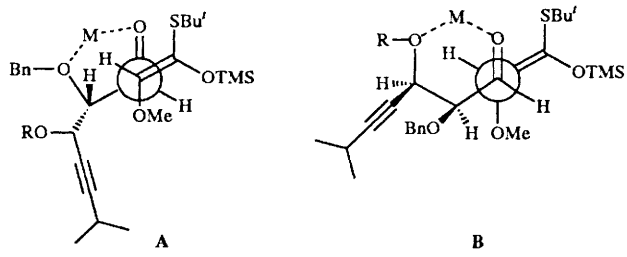
generation of a propynyl cation[10] under acidic conditions giving rise to reductive deoxygenation of the terminal tertiary hydroxy group. Hence upon treatment with octacarbonyldicobalt in methylene chloride at room temperature **13** provided the cobalt-complexed derivative **14** in 85% yield. Reductive dehydration of **14** with $NaBH_3CN$ in the presence of the zinc iodide[9] proceeded effectively, as expected, to yield the deoxygenated product **15** which was, without isolation, consecutively demetallated with cerium(IV) ammonium nitrate (CAN)[11] in methanol and desilylated with 20% hydrochloric acid to afford the desired **16** in 75% overall yield from **14**. Thus, introduction of an isopropyl group at the triple bond terminus of **12** was realised *via* the cobalt-complexed derivative **14**.

The most significant requirement for our stereocontrolled total synthesis of bengamide E **5** was obviously the stereoselective three carbon elongation of **16** for construction of the C-10 side chain analogue. In our previous synthesis[6] of bengamide E **5**, we disclosed that the aldol reaction of the aldehyde **19** with the *O*, *S*-acetal **20** under chelation-controlled conditions proceeded in a highly stereoselective manner to furnish the aldol product **22** (Scheme 2). The high



Scheme 2

stereoselectivity observed in the reaction between **19** and **20** could be tentatively interpreted in terms of the intermediacy of the transition state **A** (R = TBS) (Fig. 1). The Lewis acid ($SnCl_4$) coordinated with the aldehyde oxygen could form a five-membered transition state **A** or a six-membered transition state **B** depending on which oxygen atom, C-2 or C-3, was involved in the interaction. In the case of the aldehyde **19**, there were two distinguishable protecting groups on two hydroxy



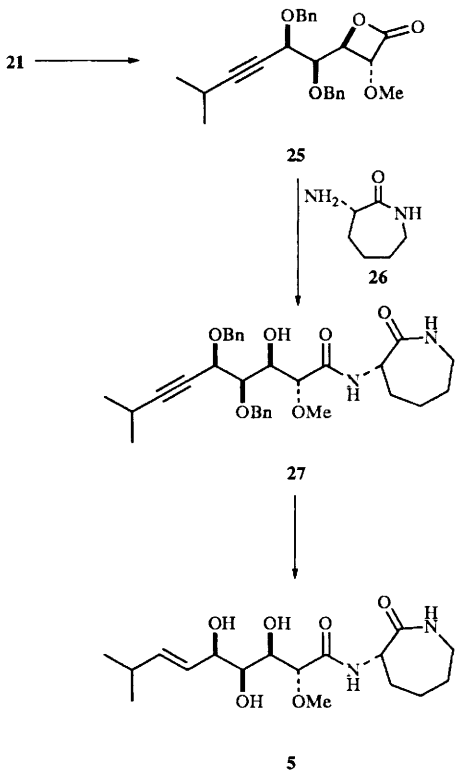
R = Bn, TBS

Fig. 1

groups: one was a benzyl group (C-2) and the other, a TBS group (C-3). The oxygen atom of a silyloxy group is generally regarded as less effective for coordination with a Lewis acid. Therefore, formation of the transition state **A** would be expected to be preferred over that of the transition state **B**. The *O*,*S*-acetal **20** would then synclinally approach the electrophilic centre of the activated aldehyde **19** in the transition state **A**, where the hydrogen atom on the double bond of the *O*,*S*-acetal **20** would be placed on the most sterically demanding position of the aldehyde counterpart to minimise unfavourable non-bonding interactions, leading to the formation of **22**.

We anticipated that the aldol reaction of the aldehyde **18**, derived from **16**, with the *O*,*S*-acetal **20** under chelation-controlled conditions might proceed *via* the transition state **A** (R = Bn) to give the thioester derivative **21** predominantly, although the possibility of concomitant production of aldol products arising from the transition state **B** (R = Bn) could not be ruled out because the aldehyde **18** has a benzyl protecting group which is able to coordinate with a Lewis acid at C-3 as well as the C-2 hydroxy group. The required *O*,*S*-acetal **20** was prepared from *S*-*tert*-butyl methoxyethanethioate according to Gennari's procedure.[12] The ratio of (*E*)- to (*Z*)-isomers of **20** was determined to be 75 to 25 by analysis of its ^1H NMR spectrum based on the literature precedent.[12,13] The primary hydroxy compound **16** was oxidised under Swern conditions to provide the corresponding aldehyde **18**. Because of its instability, **18** was directly exposed to the aldol conditions with the *O*,*S*-acetal **20** in the presence of tin(IV) chloride ($SnCl_4$) at −78 °C. Although the desired aldol product **21** could be detected in the reaction mixture, a majority of the reaction mixture consisted of several diastereoisomers of **21**.

At this point, we realised again the potential of a bulky hexacarbonyldicobalt-complexed triple bond to differentiate between the two hydroxy groups at the C-2 and C-3 positions of **18**. The transition state **B** (R = Bn) has a *cis*-relationship between the C-2 benzylated hydroxy group and the triple bond moiety on a fixed six-membered ring. Increasing the steric bulk around the sterically less hindered triple bond moiety by cobalt complexation would make the transition state **B** significantly less favourable. This would not be the case in the transition state **A** where the triple bond moiety is appended to a fixed five-membered ring. As a result, the reaction pathway through the transition state **A** would be preferred over that through the transition state **B** giving rise to predominant formation of **24**. On the basis of these considerations, we investigated the aldol reaction of the cobalt-complexed aldehyde **23**. After reductive removal of the tertiary hydroxy group of **14** with $NaBH_3CN$, the resulting deoxygenated product **15** was hydrolysed with 20% hydrochloric acid to afford **17** in 78% yield. The alcohol **17** was oxidised under Swern conditions according to Jeong's procedure,[14] to produce the corresponding aldehyde **23** with cobalt complexation, which was subsequently exposed to the aldol conditions described for the reaction of **18** with **20** leading to the exclusive formation of the cobalt-complexed aldol



Scheme 3

product **24**. Decomplexation of **24** by treatment with CAN in methanol gave **21** in 47% overall yield from **17**. It should be mentioned that no diastereoisomers could be detected in the reaction mixture. Complete stereocontrol was realised by using the cobalt-complexed aldehyde **23**.

With compound **21** possessing the requisite four stereogenic centres in hand, the stage was set for completing a total synthesis of bengamide E **5**. Upon treatment with silver(I) trifluoroacetate[15] in methanol at 45 °C, **21** underwent lactonisation to furnish the β-lactone **25**. Because of its instability **25** could not be isolated by chromatography. However, IR spectral analysis of a crude material indicated that **25** had the β-lactone structure based on the observation of an absorption band at 1840 cm^{-1}. The crude β-lactone **25**, thus obtained, was treated with (*S*)-3-aminoazepan-2-one **26** in methylene chloride in the presence of trimethylaluminium[24,e] to give the amide **27** in 75% yield from **21**. Finally Birch reduction of **27** effected debenzylation and reduction of the triple bond to the *trans*-double bond providing (+)-bengamide E **5** in 65% yield. The synthetic (+)-bengamide E was identified by comparison with the NMR and IR spectra and specific rotation of an authentic specimen.[6]

Thus, we have accomplished a highly stereocontrolled total synthesis of (+)-bengamide E from commercially accessible diisopropyl D-tartrate. It is noteworthy that in the present synthesis we took advantage of synthetically useful properties of cobalt complexation. In fact cobalt complexation enabled us not only to obtain the desired aldol product **21** in a completely stereoselective fashion, but also to remove the terminal tertiary hydroxy group of **13**.

Experimental

Mps were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$, mass spectra with Hitachi M-80 and JEOL JMS-SX 102 A mass spectrometers. ^1H NMR spectra were measured with JEOL EX-270 and JEOL JNM-GX 500 spectrometers in $CDCl_3$ using either tetramethylsilane as an internal standard for compounds that have no silyl group or $CHCl_3$ (7.26 ppm) for compounds possessing a silyl group, ^{13}C NMR spectra with JEOL EX-270 and JEOL JNM-GX 500 spectrometers in $CDCl_3$ with $CDCl_3$ (77.0 ppm) as an internal reference. All *J* values are in Hz and $[\alpha]_D$ values in 10^{-1} deg cm^2 g^{-1}. Methylene chloride was freshly distilled from P_2O_5 and THF from sodium–benzophenone ketyl prior to use. Silica gel (silica gel 60, 230–400 mesh, Nacalai Tesque) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4. The *O*-silyl ketene *O*,*S*-acetal **20** was prepared from *S*-*tert*-butyl methoxyethanethioate according to Gennari's procedure.[12]

Diisopropyl (2*S*,3*S*)-2,3-dibenzyloxysuccinate 8

A solution of diisopropyl D-tartrate **7** (234 mg, 1 mmol) in dry THF (5 cm^3) was added dropwise to a suspension of NaH (60% oil dispersion; 77 mg, 1.93 mmol) in THF (5 cm^3) at 0 °C and the THF solution was stirred for 1 h at the same temperature. Tetrabutylammonium iodide (75 mg, 0.20 mmol), a catalytic amount of 18-crown-6 (0.6 mg, 0.66 × 10^{-2} mmol) and benzyl bromide (0.23 cm^3, 1.93 mmol) were successively added to the reaction mixture. The reaction mixture was stirred for 7 h at room temperature before being quenched by addition of hydrochloric acid (1 mol dm^{-3}, 3 cm^3). The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with aq. $NaHCO_3$ and brine, dried, and concentrated to dryness. Recrystallisation of the residue from methanol afforded (−)-**8** (331 mg, 80%) as colourless solids, mp 76–77 °C (Found: C, 69.45; H, 7.4. $C_{24}H_{30}O_6$ requires C, 69.55; H, 7.29%); $[\alpha]_D^{21.5}$ −90.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 1745 and 1720 (CO); δ_H 7.32–7.25 (10 H, aromatic H), 5.05 (2 H, hept, *J* 6.3, C*H*Me_2), 4.86, 4.47 (4 H, AB-q, *J* 11.6, benzylic H), 4.39 (2 H, s, 2-H and 3-H), 1.25 (6 H, d, *J* 6.3, Me) and 1.16 (6 H, d, *J* 6.3, Me); δ_C 168.75, 137.09, 128.27, 128.23, 127.84, 78.94, 73.37, 69.17 and 21.78; *m*/*z* 323 (M^+ − 91, 6%), 221 (76), 181 (36), 161 (38), 107 (84) and 91 (100).

(2*R*,3*R*)-2,3-Dibenzyloxybutane-1,4-diol 9

To a suspension of LAH (36 mg, 0.95 mmol) in THF (2 cm^3) was added a solution of succinate **8** (233 mg, 0.56 mmol) in THF (5 cm^3) at 0 °C. The reaction mixture was heated under reflux for 3 h and then quenched by the addition of saturated aq. Na_2SO_4. The resulting precipitate was filtered off by suction and the filtrate was dried and evaporated off to leave the crude material, which was recrystallised from hexane–ethyl acetate to give (−)-**9** (151 mg, 88%) as a colourless solid, mp 45–46 °C (Found: C, 71.6; H, 7.5. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33%); $[\alpha]_D^{21.5}$ −22.5 (*c* 0.50, EtOH); ν_{max}/cm^{-1} 3600 and 3400 (OH); δ_H 7.38–7.25 (10 H, aromatic H), 4.64 (4 H, s, CH_2OH), 3.83–3.68 (6 H, m, benzylic H, 2-H and 3-H) and 2.36 (2 H, s, OH); δ_C 137.92, 128.54, 127.96, 127.92, 78.89, 72.56 and 60.79; *m*/*z* 211 (M^+ − 91, 37%), 193 (50), 181 (29), 107 (100) and 92 (92).

(2*R*,3*R*)-2,3-Dibenzyloxy-4-*tert*-butyldimethylsilyloxybutan-1-ol 10

To a suspension of NaH (60% oil dispersion; 270 mg, 5.6 mmol) in THF (11 cm^3) was added dropwise a solution of diol **9** (1.69 g, 5.6 mmol) in THF (10 cm^3) at 0 °C and the THF solution was stirred at room temperature for 1 h. A solution of TBSCl (844 mg, 5.6 mmol) in THF (10 cm^3) was added to the reaction mixture. After stirring for 3 h at room temperature, the reaction mixture was quenched by addition of aq. 10% potassium carbonate and extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with

hexane–ethyl acetate (10:1) provided (−)-**10** (2.10 g, 90%) as a colourless viscous oil (Found: C, 69.0; H, 8.7. $C_{24}H_{36}O_4Si$ requires C, 69.10; H, 8.71%); $[\alpha]_D^{21.5}$ −15.7 (*c* 0.48, $CHCl_3$); ν_{max}/cm^{-1} 3450 (OH); δ_H 7.38–7.23 (10 H, aromatic H), 4.74, 4.64 (2 H, AB-q, *J* 11.7, benzylic H), 4.67, 4.63 (2 H, AB-q, *J* 11.7, benzylic H), 3.84–3.63 (6 H, m, CH_2), 2.43 (1 H, br s, OH), 0.91 (9 H, s, SiBu^t) and 0.07 (6 H, s, $SiMe_2$); δ_C 138.33, 128.36, 128.19, 128.12, 127.94, 127.91, 127.71, 80.22, 79.30, 73.01, 72.71, 62.29, 61.37, 25.82, 18.19 and −5.48; *m*/*z* 416 (M^+, 0.2%), 325 (3), 219 (22), 181 (100) and 91 (92).

(3*R*,4*R*)-3,4-Dibenzyloxy-1,1-dibromo-5-*tert*-butyldimethylsilyloxypent-1-ene 11

A solution of dimethyl sulfoxide (0.094 cm^3, 1.33 mmol) in methylene chloride (0.5 cm^3) was added to a solution of oxalyl chloride (0.06 cm^3, 0.69 mmol) in methylene chloride (0.5 cm^3) at −78 °C. After stirring the methylene chloride solution for 15 min, a solution of alcohol **10** (137 mg, 0.33 mmol) in methylene chloride (0.5 cm^3) was added and the reaction mixture was stirred at the same temperature for 1 h. Triethylamine (0.34 cm^3, 2.44 mmol) was added to the reaction mixture, which was then gradually warmed to room temperature and diluted with methylene chloride. The methylene chloride solution was washed with water and brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel eluting with hexane–ethyl acetate (10:2) to afford the crude aldehyde.

A solution of carbon tetrabromide (210 mg, 0.64 mmol) in methylene chloride (1.5 cm^3) was added dropwise to a solution of triphenylphosphine (340 mg, 1.3 mmol) in methylene chloride (3 cm^3) at 0 °C. After stirring for 15 min triethylamine (0.045 cm^3, 0.32 mmol) was added to the reaction mixture, which was kept at the same temperature for 5 min and then cooled to −78 °C. A solution of the prepared crude aldehyde in methylene chloride (2 cm^3) was added to the reaction mixture at −78 °C. After being stirred for 5 min at the same temperature, the reaction mixture was gradually warmed to −20 °C and quenched with saturated aq. $NaHCO_3$, diluted with water and extracted with methylene chloride. The extract was washed with water and brine, dried and concentrated to dryness. The residual solids were stirred vigorously in hexane for 10 min and filtered off by suction. The filtrate was concentrated and chromatographed with hexane–ethyl acetate (50:2) to give (−)-**11** (122 mg, 65%) as a colourless oil (Found: C, 52.6; H, 6.0. $C_{25}H_{34}Br_2O_3Si$ requires C, 52.64; H, 6.01%); $[\alpha]_D^{21.5}$ −18.1 (*c* 0.44, $CHCl_3$); δ_H 7.34–7.26 (10 H, aromatic H), 6.58 (1 H, d, *J* 8.6, olefinic H), 4.70, 4.62 (2 H, AB-q, *J* 11.9, benzylic H), 4.64, 4.42 (2 H, AB-q, *J* 11.9, benzylic H), 4.27 (1 H, dd, *J* 4.0 and 8.6, 3-H), 3.75 (1 H, dd, *J* 6.3 and 10.6, 5-H), 3.69 (1 H, dd, *J* 5.6 and 10.6, 5-H), 3.51 (1 H, ddd, *J* 4.0, 5.6 and 6.3, 4-H), 0.87 (9 H, s, SiBu^t) and 0.02 (6 H, s, $SiMe_2$); δ_C 138.20, 137.83, 137.36, 128.30, 128.25, 128.09, 128.00, 127.85, 127.82, 127.67, 91.63, 80.76, −5.42 and −5.49; *m*/*z* 571 (M^+ + 1, 4%), 315 (99), 181 (100) and 91 (100).

(3*R*,4*R*)-3,4-Dibenzyloxy-5-*tert*-butyldimethylsilyloxypent-1-yne 12

To a solution of pentene **11** (547 mg, 0.96 mmol) in dry diethyl ether (10 cm^3) was added BuLi in hexane (1.6 mol dm^{-3}; 1.23 cm^3, 1.94 mmol) at 0 °C over a period of 10 min. After stirring for 5 min, the reaction mixture was quenched by addition of saturated aq. ammonium chloride, diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (100:1.5) afforded (−)-**12** (376 mg, 96%) as a colourless oil (Found: C, 73.4; H, 8.4. $C_{25}H_{34}O_3Si$ requires C, 73.13; H, 8.35%); $[\alpha]_D^{22}$ −28.5 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} 3310 (C≡CH); δ_H 7.41–7.24 (10 H, aromatic H), 4.84, 4.76 (2 H, AB-q, *J* 11.7, benzylic H), 4.80, 4.55 (2 H, AB-q, *J* 11.7, benzylic H), 4.30 (1 H, dd, *J* 2.0 and 5.5, 3-H), 3.91 (1 H, dd, *J* 4.4 and 10.7, 5-H), 3.79 (1 H, dd, *J* 6.4 and 10.7, 5-H), 3.66 (1 H, ddd, *J* 4.4, 5.5 and 6.4, 4-H), 2.50 (1 H, d, *J* 2.0, C≡CH), 0.87 (9 H, s, SiBu^t) and 0.03 (6 H, s, $SiMe_2$); δ_C 138.63, 137.63, 128.30, 128.19, 127.96, 127.66, 127.49, 81.35, 80.61, 75.17, 73.68, 71.00, 68.70, 62.98, 25.88, 18.24, −5.41 and −5.44; *m*/*z* 410 (M^+, 0.1%), 213 (19), 181 (100), 155 (81), 117 (99) and 91 (89).

(5*R*,6*R*)-5,6-Dibenzyloxy-6-*tert*-butyldimethylsilyloxy-2-methylhept-3-yn-2-ol 13

To a solution of pentyne **12** (656 mg, 1.60 mmol) in THF (10 cm^3) was added dropwise BuLi in hexane (1.6 mol dm^{-3}; 2.1 cm^3, 3.35 mmol) at −78 °C. After stirring for 1 h, acetone (1.17 cm^3, 16 mmol) was added to the reaction mixture over a period of 5 min and stirring was continued for 3 h at −78 °C. The reaction mixture was quenched by addition of saturated aq. $NaHCO_3$, diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (25:1) gave (−)-**13** (629 mg, 84%) as a colourless oil (Found: C, 71.6; H, 8.6. $C_{28}H_{40}O_4Si$ requires C, 71.75; H, 8.60%); $[\alpha]_D^{22}$ −34.0 (*c* 0.24, $CHCl_3$); ν_{max}/cm^{-1} 3600 and 3400 (OH); δ_H 7.37–7.23 (10 H, aromatic H), 4.80, 4.75 (2 H, AB-q, *J* 12.0, benzylic H), 4.78, 4.55 (2 H, AB-q, *J* 11.9, benzylic H), 4.32 (1 H, d, J 5.0, 5-H), 3.88 (1 H, dd, *J* 4.6 and 10.6, 7-H), 3.75 (1 H, dd, *J* 6.3 and 10.6, 7-H), 3.63 (1 H, ddd, *J* 4.6, 5.0 and 6.3, 6-H), 1.91 (1 H, br s, OH), 1.52 (6 H, s, Me_2), 0.87 (9 H, s, SiBu^t) and 0.02 (6 H, s, $SiMe_2$); δ_C 138.69, 137.88, 128.25, 128.19, 127.92, 127.78, 127.58, 127.48, 91.79, 81.62, 78.89, 73.64, 71.05, 68.88, 65.12, 62.91, 31.34, 31.30, 25.88, 18.24, −5.41 and −5.44; *m*/*z* 450 (M^+ − 18, 1%), 273 (13), 181 (36), 117 (100) and 91 (96).

Hexacarbonyl-μ-[(5*R*,6*R*)-5,6-dibenzyloxy-7-*tert*-butyldimethylsilyloxy-2-hydroxy-2-methyl-1κ*C*^{3},1κ*C*^{4}:2κ*C*^{3},2κ*C*^{4}-heptane-3,3,4,4-tetrayl]dicobalt (*Co*–*Co*) 14

A solution of heptynol **13** (120 mg, 0.25 mmol) in methylene chloride (5 cm^3) was added dropwise to a stirred solution of octacarbonyldicobalt (88 mg, 0.26 mmol) in methylene chloride (5 cm^3). The reaction mixture was stirred at room temperature for 3 h and then the methylene chloride was evaporated off. The residue was chromatographed with hexane–ethyl acetate (40:1) to afford **14** (164 mg, 85%) as a deep brown oil (Found: C, 54.2; H, 5.4. $C_{34}H_{40}Co_2O_{10}Si$ requires C, 54.16; H, 5.34%); ν_{max}/cm^{-1} 3400 (OH), 2080 (C≡O), 2040 (C≡O) and 1995 (C≡O); δ_H 7.40–7.20 (10 H, aromatic H), 4.87, 4.74 (2 H, AB-q, *J* 11.7, benzylic H), 4.66–4.59 (3 H, m, benzylic H and 5-H), 4.00 (1 H, dd, *J* 2.0 and 10.7, 7-H), 3.95 (1 H, ddd, *J* 2.0, 5.4 and 7.3, 6-H), 3.83 (1 H, dd, *J* 7.3 and 10.7, 7-H), 1.49 (3 H, s, Me), 1.45 (3 H, s, Me), 0.92 (9 H, s, SiBu^t), 0.07 (3-H, s, SiMe) and 0.06 (3 H, s, SiMe); δ_C 200.13, 137.21, 137.00, 128.79, 128.57, 128.37, 128.28, 128.08, 127.90, 81.03, 79.53, 73.93, 73.00, 72.10, 63.82, 32.22, 31.11, 25.85, 18.15, −5.38 and −5.54; FAB mass *m*/*z* 670 (M^+ − 84, 22), 181 (11), 108 (28) and 91 (100). Specific rotation could not be determined because demetallation occurred during measurement.

(2*R*,3*R*)-2,3-Dibenzyloxy-6-methylhept-4-yn-1-ol 16

To a solution of cobalt complex **14** (193 mg, 0.26 mmol) in methylene chloride (10 cm^3) was successively added zinc iodide (483 mg, 1.51 mmol) and $NaBH_3CN$ (314 mg, 5.0 mmol) at room temperature. After stirring for 7 h, the reaction mixture was passed through a short pad of Celite. The filtrate was concentrated to dryness and the resulting cobalt complex **15** was dissolved in methanol (10 cm^3) and cooled to 0 °C, to which CAN (562 mg, 1.03 mmol) was added portionwise. The reaction

mixture was stirred for 1 h at 0 °C and then 20% hydrochloric acid (2 cm^3) was added. The reaction mixture was stirred for 2 h at room temperature and then the methanol was evaporated off. The residue was taken up in ethyl acetate, the solution washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (10:1) gave (−)-**16** (65 mg, 75%) as a colourless oil (Found: C, 77.9; H, 7.8. $C_{22}H_{26}O_3Si$ requires C, 78.08; H, 7.74%); $[\alpha]_D^{21.5}$ −55.0 (*c* 1.07, $CHCl_3$); ν_{max}/cm^{-1} 3500 (OH) and 2240 (C≡C); δ_H 7.36–7.25 (10 H, aromatic H), 4.87, 4.65 (2 H, AB-q, *J* 11.6, benzylic H), 4.83, 4.54 (2 H, AB-q, *J* 11.9, benzylic H), 4.30 (1 H, dd, *J* 2.0 and 6.3, 3-H), 3.85 (1 H, dd, J 3.9 and 11.2, 1-H), 3.71 (1 H, dd, *J* 5.9 and 11.2, 1-H), 3.68 (1 H, ddd, *J* 3.9, 5.9 and 6.3, 2-H), 2.62 (1 H, dhept, *J* 2.0 and 6.9, 6-H), 2.58 (1 H, br s, OH) and 1.20 (6 H, d, *J* 6.9, Me_2); δ_C 138.81, 137.77, 128.43, 128.37, 127.96, 127.80, 127.71, 94.56, 80.96, 74.88, 73.60, 70.70, 70.59, 62.52, 22.90, 22.68 and 20.60; *m/z* 338 (M^+, 0.5%), 229 (50), 205 (51), 187 (100) and 92 (99).

Hexacarbonyl-μ-[(5*R*,6*R*)-5,6-dibenzyloxy-7-hydroxy-2-methyl-1κ*C*^{3},1κ*C*^{4}:2κ*C*^{3},2κ*C*^{4}-heptane-3,3,4,4-tetrayl]dicobalt (*Co–Co*) 17

According to the procedure described for the conversion of **14** into **16**, cobalt complex **14** (193, 0.26 mmol) was treated with zinc iodide (483 mg, 1.51 mmol) and $NaBH_3CN$ (314 mg, 5.0 mmol) to give the crude **15**, to a THF solution (20 cm^3) of which was added 20% hydrochloric acid (5 cm^3). The reaction mixture was stirred at room temperature for 2 h and then concentrated. The residue was taken up in ethyl acetate, the solution washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (50:1) provided **17** (125 mg, 78%) as a deep brown oil (Found: C, 53.7; H, 4.2. $C_{28}H_{26}Co_2O_9$ requires C, 53.86; H, 4.20%); ν_{max}/cm^{-1} 3500 (OH), 2080 (C≡O), 2040 (C≡O) and 1990 (C≡O); δ_H 7.44–7.16 (10 H, aromatic H), 4.83–4.58 (5 H, m, benzylic H and 5-H), 3.85 (1 H, m, 7-H), 3.72–3.59 (2 H, m, 6-H and 7-H), 3.02 (1 H, m, 2-H), 2.12 (1 H, br s, OH), 1.22 (3 H, d, *J* 6.8, Me) and 1.20 (3 H, d, *J* 6.4, Me); δ_C 200.02, 137.83, 137.75, 128.45, 128.34, 128.09, 127.92, 127.67, 108.43, 93.12, 82.75, 79.86, 74.05, 73.48, 61.83, 31.97, 24.46 and 24.37; *m/z* (FAB) 568 (M^+ − 56, 26%), 540 (66), 456 (100), 226 (100), 151 (95) and 91 (100). Specific rotation could not be determined because demetallation occurred during the measurement.

***S-tert*-Butyl (2*R*,3*S*,4*R*,5*R*)-4,5-Dibenzyloxy-3-hydroxy-2-methoxy-8-methylnon-6-ynethioate 21**

According to the procedure described for the conversion of **10** into **11**, cobalt complex **17** (126 mg, 0.20 mmol) was oxidised under the Swern conditions. The resulting residue was passed through a short pad of silica gel with hexane–methylene chloride (2:1) to afford cobalt complex **23**. To a solution of crude **23** in methylene choride (6 cm^3) was successively added a solution of thioester **20** (78 mg, 0.33 mmol) in methylene chloride (0.5 cm^3) and a solution of $SnCl_4$ in methylene chloride (1 mol dm^{-3}; 0.33 cm^3, 0.33 mmol) at −78 °C. The reaction mixture was stirred for 20 min and gradually warmed to 0 °C. The reaction mixture was quenched by addition of saturated aq. ammonium chloride, diluted with water and extracted with methylene chloride. The extract was washed with water and brine, dried and concentrated to give cobalt complex **24**, which was then dissolved in methanol (5 cm^3). To a cooled methanol solution of **24** at 0 °C was added CAN (438 mg, 0.80 mmol) and the reaction mixture was stirred for 45 min at the same temperature. The methanol was evaporated off and the residue was taken up in ethyl acetate, the solution washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–ethyl acetate (20:1) afforded (+)-**21** (47 mg, 47%) as a colourless oil (Found: C, 69.7; H, 7.9. $C_{29}H_{38}O_5S$ requires C, 69.85; H, 7.68%); $[\alpha]_D^{22}$ +5.1 (*c* 0.60, $CHCl_3$); ν_{max}/cm^{-1} 3500 (OH) and 1675 (C=O); δ_H 7.40–7.25 (10 H, aromatic H), 4.99, 4.66 (2 H, AB-q, *J* 11.2, benzylic H), 4.85, 4.55 (2 H, AB-q, *J* 11.5, benzylic H), 4.42 (1 H, dd, *J* 2.0 and 7.9, 5-H), 4.13 (1 H, ddd, *J* 1.0, 7.9 and 8.9, 3-H), 3.83 (1 H, dd, *J* 1.0 and 7.9, 4-H), 3.55 (1 H, d, *J* 7.9, 2-H), 3.25 (3 H, s, OMe), 2.61 (1 H, dhept, *J* 2.0 and 6.9, 8-H), 2.59 (1 H, d, *J* 8.9, OH), 1.48 (9 H, s, Bu^t) and 1.20 (6 H, d, *J* 6.9, Me_2); δ_C 201.99, 138.35, 137.99, 128.34, 128.28, 127.94, 127.73, 127.57, 94.88, 87.76, 79.01, 75.19, 74.81, 72.08, 71.99, 71.07, 58.47, 47.55, 30.03, 29.80, 29.67, 22.84 and 20.61; *m/z* (FAB) 499 (M^+ + 1, 1%), 185 (6) and 91 (100).

(2*R*,3*S*,4*R*,5*R*)-4, 5-Dibenzoyloxy-3-hydroxy-2-methoxy-8-methyl-*N*-[(3*S*)-2-oxoazepan-3-yl]non-6-ynamide 27

To a solution of thioester **21** (84 mg, 0.17 mmol) in methanol (5 cm^3) at room temperature was added silver(I) trifluoroacetate (220 mg, 1.0 mmol) and the reaction mixture was heated at 45 °C for 5 h (disappearance of **21** was monitored by TLC). The reaction mixture was allowed to cool and then a few drops of saturated aq. ammonium chloride were added to it and the resulting precipitates were filtered off by suction. The filtrate was concentrated to leave the crude **25**, which was used for the next reaction. To a solution of azepanone (−)-**26** (69 mg, 0.54 mmol) in methylene chloride (1 cm^3) was added dropwise trimethylaluminium in hexane (2 mol dm^{-3}; 0.54 cm^3, 1.08 mmol) at 0 °C and the reaction mixture was stirred for 15 min at room temperature and then cooled to 0 °C. A solution of lactone **25** in methylene chloride (1.5 cm^3) was added dropwise to the reaction mixture at 0 °C, which was gradually warmed to room temperature, and then heated at 45 °C for 5 h. After cooling to 0 °C, the reaction mixture was diluted with saturated aq. Rochelle's salt (3 cm^3) and vigorously stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined methylene chloride layers were washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with methylene chloride–methanol (10:1) gave (−)-**27** (68 mg, 75%) as colourless needles, mp 155–156 °C (from ethyl acetate) (Found: C, 69.5; H, 7.5; N, 5.2. $C_{31}H_{40}N_2O_6$ requires C, 69.38; H, 7.51; N, 5.22%); $[\alpha]_D^{22.5}$ −26.1 (*c* 0.60, MeOH); ν_{max}/cm^{-1} 3400 (OH and NH) and 1660 (C=O); δ_H 7.81 (1 H, d, *J* 6.3, NH), 7.40–7.25 (10 H, aromatic H), 6.24 (1 H, t, *J* 6.6, NH), 5.02, 4.64 (2 H, AB-q, *J* 10.9, benzylic H), 4.84, 4.56 (2 H, AB-q, *J* 11.6, benzylic H), 4.49 (1 H, dd, *J* 1.7 and 7.6, 5-H), 4.12 (1 H, ddd, *J* 2.0, 6.9 and 7.6, 3-H), 3.86 (1 H, dd, *J* 2.0 and 7.6, 4-H), 3.76 (1 H, d, *J* 7.6, 2-H), 3.40 (1 H, d, *J* 6.9, OH), 3.29 (3 H, s, OMe), 3.13–3.07 (2 H, m, NCH_2), 2.62 (1 H, dhept, *J* 1.7 and 6.9, 8-H), 2.11–1.23 (6 H, m, CH_2) and 1.19 (6 H, d, *J* 6.9, Me_2); δ_C 175.17, 170.58, 138.35, 138.04, 128.25, 128.09, 127.62, 127.57, 94.61, 81.28, 80.02, 75.26, 75.02, 72.09, 71.84, 70.91, 58.40, 51.97, 41.89, 31.25, 28.81, 27.89, 22.88 and 20.63; *m/z* FAB 538 (M^+ + 2, 18%), 229 (7), 155 (18) and 91 (100).

(2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8-methyl-*N*-[(3*S*)-2-oxoazepan-3-yl]non-6-enamide (bengamide E) 5

To a solution of nonynamide **27** (30 mg, 0.056 mmol) in THF (2 cm^3) was added liquid ammonia (*ca.* 20 cm^3) and sodium metal (100 mg, 0.40 mmol) at −78 °C. The reaction mixture was allowed to stand for 30 min at the same temperature. Solid ammonium chloride was added to the reaction mixture, which was then gradually warmed to room temperature. The residue was taken up in ethyl acetate, the solution washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with chloroform–methanol (20:1) to furnish (+)-**5** (13 mg, 65%) as a colourless viscous oil (Found: M^+ 359.2217. $C_{17}H_{31}N_2O_6$ requires *m/z* 359.2182); $[\alpha]_D^{22}$ +26.0 (*c* 0.29, MeOH {lit.,[6] $[\alpha]_D^{22}$ +24.0 (*c* 0.1, MeOH)}; ν_{max}/cm^{-1} 3400

(OH and NH) and 1660 (C=O); δ_H 7.97 (1 H, d, *J* 5.9, NH), 6.17 (1 H, t, *J* 5.9, NH), 5.79 (1 H, ddd, *J* 1.0, 5.9 and 16.0, 7-H), 5.45 (1 H, ddd, *J* 1.0, 7.3 and 16.0, 6-H), 4.54 (1 H, dd, *J* 5.9 and 10.0, NCHCO), 4.22 (1 H, br s, 5-H), 3.82 (1 H, dd, *J* 1.5 and 7.3, 3-H), 3.79 (1 H, d, *J* 7.3, 2-H), 3.60 (1 H, dd, *J* 1.5 and 5.4, 4-H), 3.54 (3 H, s, OMe), 3.36–3.22 (2 H, m, CH_2N), 2.37–2.26 (1 H, m, 8-H), 2.12–1.36 (6 H, m, CH_2), 1.00 (3 H, d, *J* 6.8, Me) and 1.00 (6 H, d, *J* 6.8, Me); δ_C 174.70, 172.12, 141.83, 125.37, 80.88, 74.27, 72.79, 72.38, 59.97, 52.01, 42.12, 31.05, 30.79, 28.84, 27.94, 22.19 and 22.09; *m/z* (FAB) 359 ($M^+ + 1$, 5%), 277 (10), 185 (94) and 93 (100).

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