PERKIN 1

Studies on synthesis of optically active twelve-membered diynes: a convergent construction of a twelve-membered diketodiyne compound with C_2 symmetry

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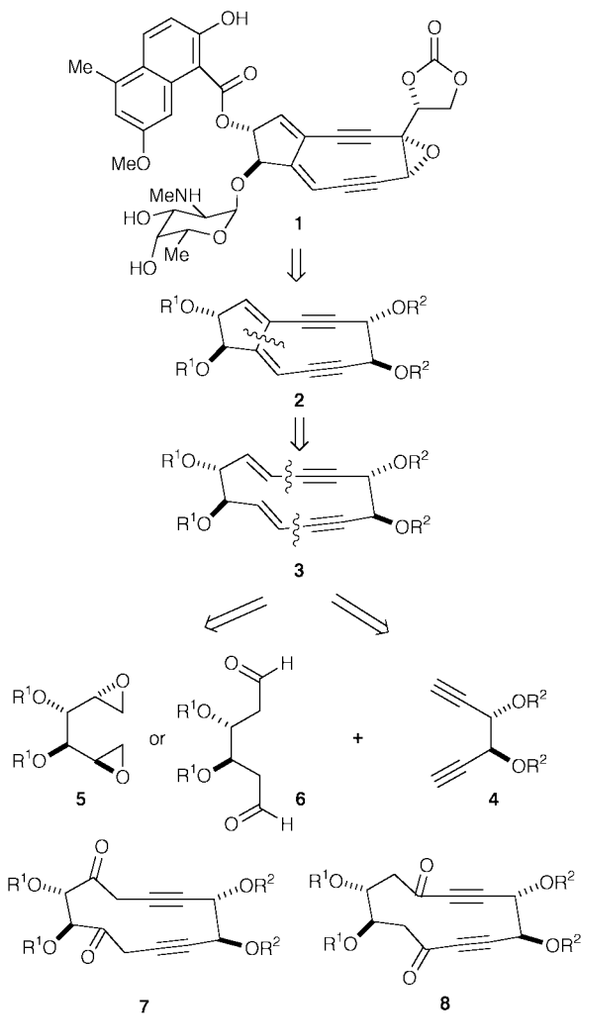
Received (in Cambridge, UK) 16th November 1999, Accepted 20th December 1999
Published on the Web 7th February 2000

A convergent procedure for the preparation of optically active twelve-membered diketodiyne derivatives with C_2 symmetry possessing four hydroxy functionalities was developed starting from the commercially available diethyl L-tartrate. The key step for the construction of the twelve-membered diyne framework involved an intramolecular chromous chloride-mediated coupling reaction between the aldehyde functionality and the alkyne moiety having an iodine atom at its terminus.

Introduction

Neocarzinostatin (NCS), an antitumor antibiotic, was first isolated from *Streptomyces carzinostaticus* var F-41 by Ishida *et al*. in 1965.[1] In 1985, the chromophoric component of NCS was shown to have a novel bicyclo[7.3.0]dodecadienediyne as a basic skeleton.[2] The related antitumor antibiotics with a similar strained core framework such as kedarcidin,[3] C-1027,[4] maduropeptin,[5] and N1999-A2[6] have been isolated. Because of the unprecedented unique structure as well as the striking biological activities, much effort has so far been concentrated on the synthesis of the NCS chromophore (**1**)[7] and its homologs.[8] The NCS chromophore (**1**) can be simplified by ring opening of the epoxy moiety leading to **2** (Scheme 1). The subsequent carbon–carbon bond fission between C-1 and C-9 of **2** would result in the twelve-membered simpler dienediyne derivative **3** with C_2 symmetry.[9] We envisioned that this type of twelve-membered compound[10] would be synthesized by two methods: namely, (i) a coupling reaction of the diyne **4** with the diepoxide **5**, and (ii) by a coupling reaction of **4** with the dialdehyde **6**. Thus, compound **3** would be regarded as the significant synthetic intermediate for the construction of the bicyclo[7.3.0]dodecadienediyne skeleton. On the basis of these predictions, the diketodiyne derivatives **7** and **8**, both of which have C_2 symmetry structure, became our target molecules which would be further manipulated into the corresponding bicyclo[7.3.0]dodecadienediyne *via* intramolecular aldol type condensation between the C-1 and C-9 positions. In this paper, we describe some results on the synthesis of the optically active twelve-membered diketodiyne derivative with C_2 symmetry.

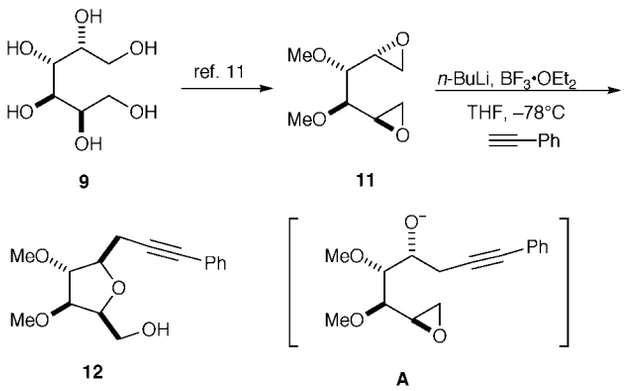


Scheme 1

Results and discussion

For the initial evaluation of this strategy, our effort was focused on the development of an efficient method for the construction of **7** starting from inexpensive D-mannitol (**9**) and diethyl L-tartrate (**10**). At the outset, D-mannitol (**9**) was converted into the C_2 symmetric known diepoxide **11**[11] (Scheme 2) possessing the vicinal two methoxy functionalities that would be suitable for our purpose. The reactivity of **11** towards acetylide was preliminarily estimated under the Yamaguchi's conditions.[12] Thus, treatment of **11** with the acetylide, prepared from the reaction of phenylacetylene with *n*-butyllithium (*n*-BuLi) in THF in the presence of boron trifluoride–diethyl ether (BF_3·OEt_2) at −78 °C, unexpectedly afforded the tetrahydrofuran derivative **12** in 62% yield. The formation of **12** could be interpreted in terms of the ring opening of one of two epoxides by the acetylide in the manner of S_N2-type displacement[13] producing the secondary alkoxide species **A** which would then intramolecularly attack the remaining epoxide functionality in

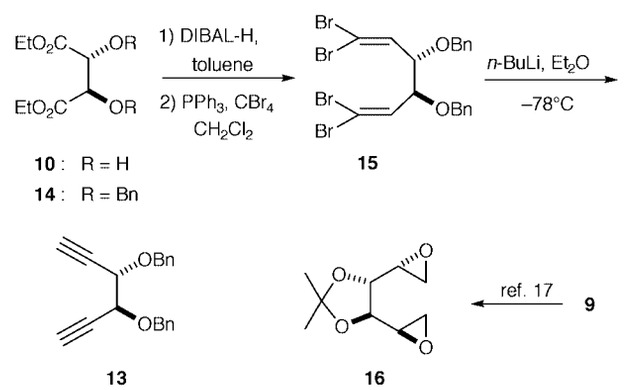
DOI: 10.1039/a909089d



Scheme 2

a 5-*exo* mode fashion[14] leading to the formation of **12**. This result strongly indicated that the 3,4-vicinal hydroxy functionality of the starting material **9** should be protected as some suitable cyclic structure such as an acetonide where two appendages should have a *trans* relationship. As a result, the unfavorable tetrahydrofuran ring formation observed in the reaction of **11** with phenylacetylide would be avoided.

The diyne counterpart **13** for the coupling reaction was prepared from diethyl L-tartrate (**10**) as follows: the known diethyl *O*,*O*-dibenzyltartrate (**14**), derived from **10** according to the literature,[15] was reduced with diisobutylaluminium hydride (DIBAL-H) to afford a labile dialdehyde, which was subsequently exposed to Corey's dibromo-olefination conditions[16] (PPh_3, CBr_4) to provide **15** in 61% yield. The required diyne **13** was then obtained in 68% yield by exposure of **15** to *n*-BuLi in Et_2O. The diepoxide compound **16** possessing the dioxolane skeleton, which is assumed to be a suitable substrate for our purpose on the basis of previous results, was easily prepared from **9** according to the literature[17] (Scheme 3).



Scheme 3

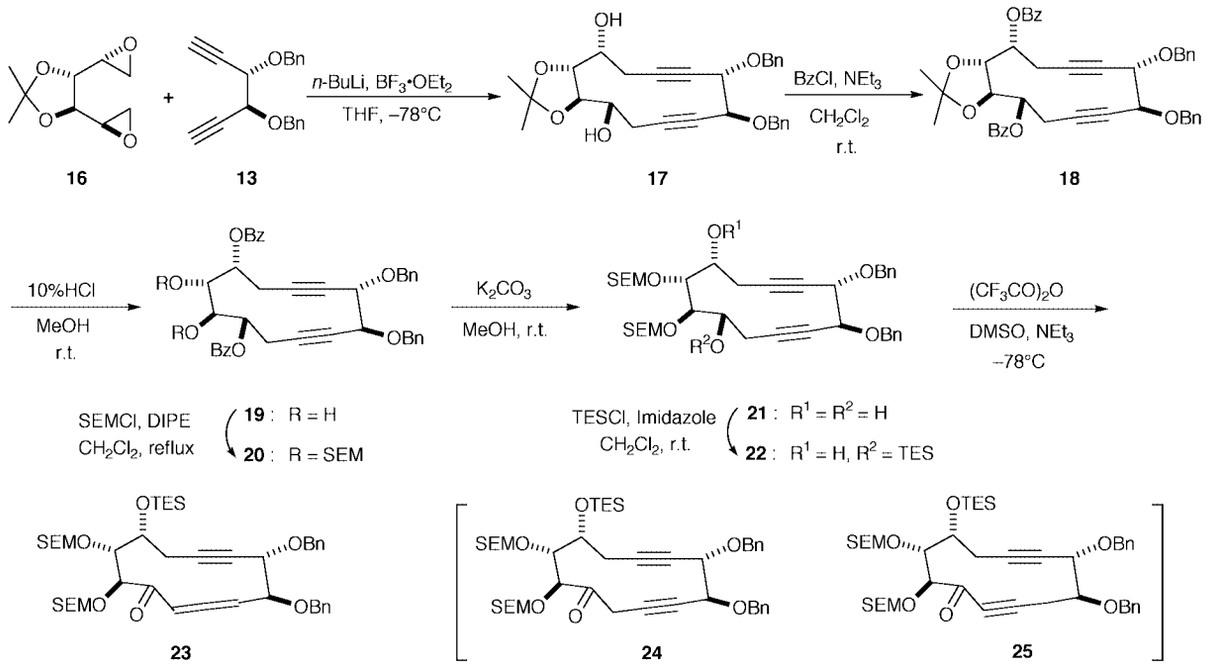
We attempted the coupling reaction between the diyne compound **13** and the diepoxide derivative **16** (with C_2 symmetry) under Yamaguchi's conditions in order to construct the twelve-membered ring **17** (Scheme 4).[12] Treatment of the diyne **13** with *n*-BuLi in THF at −78 °C gave the corresponding lithium acetylide, which was subsequently exposed to $BF_3{\cdot}OEt_2$. The resulting borane reagent was reacted with the diepoxide **16** at the same temperature to produce the twelve-membered compound **17** in 30% yield. Although the chemical yield was not satisfactory, we could obtain the twelve-membered compound **17** with C_2 symmetry. Therefore, our efforts were then directed towards oxidation of **17** to the corresponding diketo derivative compound **7** depicted in Scheme 1. However, a variety of oxidation conditions afforded only intractable mixtures. No desired compound could be detected in the reaction mixture. At this stage, we tentatively assumed that the dioxolane ring, in other words, the *trans*-fused five-membered ring would make the resulting diketone structure rather unstable leading to intractable mixtures. Changing the protecting group at the vicinal C-10 and C-11 positions[18] from a cyclic species (dioxolane) to an acyclic one, therefore, is necessary to achieve the transformation of **17** into the diketodiyne compound.

The two hydroxy groups of **17** were temporarily protected with a benzoyl group under conventional conditions to furnish the dibenzoylated compound **18** in 66% yield, which was hydrolyzed with 10% hydrochloric acid in methanol producing the diol **19** in 70% yield along with the recovery of the starting material **18** (11%). Introduction of the (trimethylsilyl)ethoxymethyl (SEM) group, an acyclic group protecting the vicinal C-10 and C-11 hydroxy groups[18] of **19**, was realized by exposure to SEM chloride in methylene chloride in the presence of diisopropylethylamine (DIPEA) at refluxing temperature to give **20** in 79% yield. Upon treatment with potassium carbonate in methanol at room temperature, **20** underwent debenzoylation producing the diol **21** in 87% yield. The stage was again set for examination of the oxidation of the diol moiety to the corresponding diketo derivative. Thus the diol **21** was exposed to several oxidation conditions as in the case of the oxidation of **17**. However, it did not take long to realize that **21** was not a suitable substrate for these oxidation conditions either.

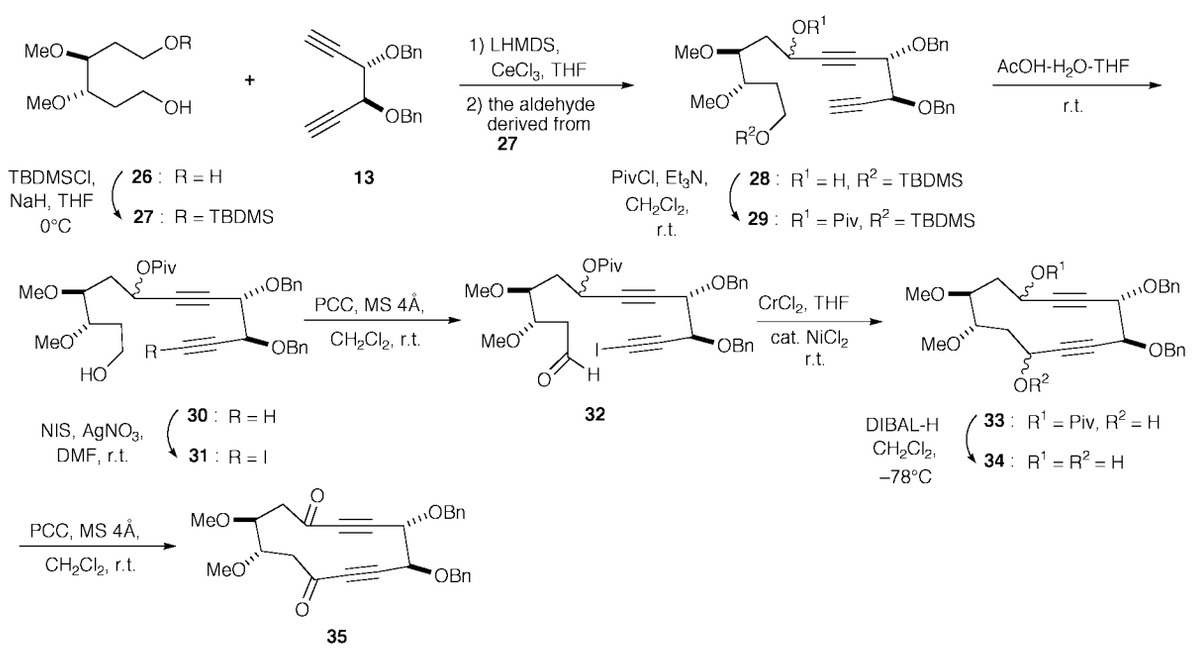
We tentatively interpreted the above results as follows: there are two hydroxy groups in **21**, one of which might be oxidized first to afford the keto-alcohol derivative. The remaining hydroxy group of the thus-formed keto-alcohol derivative may attack the carbonyl moiety, before being oxidized, resulting in the formation of the five-membered cyclic acetal species which further collapses under the oxidation conditions to form several undesired compounds. On the basis of these assumptions, we next tried to convert **21** into the mono-protected alcohol derivative. The diol **21** was treated with one equivalent of triethylsilyl (TES) chloride in methylene chloride in the presence of imidazole at room temperature to furnish the desired mono-protected alcohol **22** in 38% yield together with recovery of the starting material **21** in 52% yield. We now faced again the examination of the transformation of the hydroxy compound thus prepared into the corresponding keto derivative. After several oxidation conditions were screened, we finally found that oxidation with dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride provided the keto derivative in 81% yield. The isolated compound from the reaction mixture was, however, found not to be our desired diynone derivative **24**, but the allenic keto derivative **23**,[19] presumably produced through isomerization[20] from the former during the oxidation reaction. Since it seemed that isomerization of **23** into the undesired **25** would be much easier than that into the desired **24**, we turned our endeavor to the preparation of an alternative twelve-membered diketodiyne **8**.

According to our retrosynthetic analysis (Scheme 1), we next investigated a coupling reaction of the diyne **4** with a chiral dialdehyde with C_2 symmetry (*e.g.*, an antipode of **6**). Diethyl L-tartrate (**10**) was converted into the known dihydroxy compound **26**,[21] which was subsequently treated with *tert*-butyldimethylsilyl (TBDMS) chloride in THF in the presence of sodium hydride (NaH) to afford **27** in 71% yield (Scheme 5). The coupling reaction of the diyne **13** with the aldehyde freshly derived from **27** was carried out as follows: treatment of **13** with lithium hexamethyldisilazide (LHMDS) in THF at −78 °C in the presence of anhydrous cerium(III) chloride ($CeCl_3$)[22] generated the dicerium acetylide *in situ*, which was then exposed to the aldehyde, obtained from **27** by Swern oxidation, affording **28** in 65% yield as a mixture of two diastereoisomers in a ratio of 59:41. The resulting secondary hydroxy group of **28** was protected with pivaloyl chloride to provide **29** in 83% yield. Removal of the TBDMS group of **29** was realized by treatment with acetic acid to afford **30** in 90% yield.

After several attempts to construct the twelve-membered framework from **30** *via* the corresponding aldehyde, we finally



Scheme 4



Scheme 5

found that chromous chloride ($CrCl_2$)-mediated ring closure[23] was effective. Thus, **30** was converted into the iodo derivative **31** in 88% yield by exposure to *N*-iodosuccinimide (NIS) in the presence of silver nitrate.[24] The primary alcohol of **31** was then oxidized with pyridinium chlorochromate (PCC) to provide the corresponding aldehyde **32** in 93% yield. The stage was now set for the examination of the ring closure mediated by $CrCl_2$.[23] The aldehyde **32** was reacted with 10 equivalents of $CrCl_2$ in THF in the presence of a catalytic amount of $NiCl_2$ (5 mol%) at room temperature for 24 h to afford the desired twelve-membered compound **33** in 54% yield. Treatment of **33** with DIBAL-H effected removal of the pivaloyl group to leave the diol **34**[25] in 94% yield. The final phase in this procedure concerned the oxidation of the dihydroxy moieties of the twelve-membered diyne derivative **34**. In the cases of the twelve-membered derivatives **17** and **21** possessing dihydroxy functionalities, as previously mentioned (Scheme 4), oxidation under a variety of conditions produced only intractable mixtures. In addition, although we were able to oxidize the hydroxy group of **22**, the compound isolated from the reaction mixture was not our desired **24**, but **23** in which isomerization of the isolated acetylenic moiety to the conjugated allenic structure had occurred (*vide supra*). Therefore, it was not clear at this stage if **34** would be oxidized to give the diketodiyne compound **35**. However, PCC oxidation of **34** fortunately proceeded without any difficulty to afford the diketodiyne derivative **35** with C_2 symmetry in 81% yield. We are still uncertain about the differences in the reactivity of the oxidizing agents with **34** and the other twelve-membered dihydroxy derivatives **17** and **21**.

In summary, we have developed a procedure for the preparation of the optically active twelve-membered diketodiyne derivative **35** with C_2 symmetry starting from the commercially

available diethyl L-tartrate (**10**). Since the diketodiyne derivative **35** possesses two benzoyloxy groups at the C-4 and C-5 positions from which the epoxy functionality may be formed, it is regarded as a suitable precursor for the bicyclo[7.3.0]dodecadienediyne framework, a core of the NCS chromophore **1**. Attempts to improve the chemical yields of **35** from **10** and to convert **35** into the corresponding bicyclo[7.3.0]dodecadienediyne through aldol-type condensation[26] are now in progress.

Experimental

IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$ and mass spectra with Hitachi M-80 and JEOL JMS-SX 102 A mass spectrometers. ^{1}H NMR spectra were recorded on JEOL EX-270 and JEOL JNM-GX 500 spectrometers, using $CDCl_3$ as solvent and either tetramethylsilane as internal standard for compounds that have no silyl group, or $CHCl_3$ (7.26 ppm) for compounds possessing the silyl group. ^{13}C NMR spectra were recorded on 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 $[a]_D$ values in 10^{-1} deg cm^2 g^{-1}. CH_2Cl_2 was freshly distilled from P_2O_5, and THF, toluene and Et_2O from sodium–benzophenone prior to use. All reactions were carried out under a nitrogen atmosphere. Silica gel (Silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

(2*R*,3*S*,4*S*,5*S*)-5-Hydroxymethyl-3,4-dimethoxy-2-(3-phenylprop-2-yn-1-yl)tetrahydrofuran (−)-12

A solution of *n*-BuLi in hexane (1.41 mol dm^{-3}; 0.58 cm^3, 0.82 mmol) was added to a solution of phenylacetylene (84.0 mg, 0.82 mmol) in THF (5.5 cm^3) at −78 °C. After being stirred for 10 min, BF_3·OEt_2 (0.10 cm^3, 0.82 mmol) was added to the reaction mixture and stirring was continued for 10 min at the same temperature. A solution of **11** (47.8 mg, 0.27 mmol) in THF (1.5 cm^3) was then added to the reaction mixture, which was further stirred for 1 h, quenched by addition of saturated aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (3:1) to give (−)-**12** (47.2 mg, 62%) as a colorless oil (Found: M$^+$, 276.1361. $C_{16}H_{20}O_4$ requires *M*, 276.1362); $[a]_D^{26}$ −2.6 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3524 (OH) and 2225 (C≡C); δ_H 7.42–7.40 (2H, m, aromatic H), 7.30–7.26 (3H, m, aromatic H), 4.13–4.03 (2H, m, 2-H and 5-H), 3.89–3.83 (4H, m, 3-H, 4-H and C-5-CH_2), 3.46 (3H, s, OMe), 3.44 (3H, s, OMe), 2.83 (1H, dd, *J* 17.1 and 4.9, C-2-CH), 2.75 (1H, dd, *J* 17.1 and 8.3, C-2-CH) and 2.34 (1H, br s, OH); δ_C 131.6, 128.2, 127.9, 123.4, 86.6, 86.4, 85.8, 82.3, 81.0, 80.5, 61.6, 57.7, 57.4 and 24.5; *m*/*z* 276 (M$^+$, 24%), 244 (69), 213 (60), 115 (65) and 99 (100).

(3*S*,4*S*)-3,4-Bis(benzyloxy)-1,1,6,6-tetrabromohexa-1,5-diene (+)-15

To a solution of **14** (7.00 g, 18.1 mmol) in toluene (36 cm^3) was added a solution of DIBAL-H in hexane (40.4 cm^3, 0.95 mol dm^{-3}; 38.0 mmol) at −78 °C. The reaction mixture was kept for 1 h at the same temperature. To a solution of PPh_3 (28.5 g, 108 mmol) in CH_2Cl_2 (50 cm^3) was added a solution of CBr_4 (18.0 g, 54.3 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C and the solution was stirred for an additional 10 min. A solution of the crude dialdehyde derivative, freshly prepared from **14** in toluene, was then added to a solution of the ylide in CH_2Cl_2 solution at −78 °C. The reaction mixture was then gradually warmed to rt and stirring was continued for 16 h at rt, quenched by addition of saturated aq. Na_2SO_4 and filtered. The filtrate was passed through a short pad of silica gel with CH_2Cl_2 in order to remove triphenylphosphine oxide. The residue was chromatographed with hexane–AcOEt (50:1) to give (+)-**15** (6.69 g, 61%) as a pale yellow oil (Found: C, 39.2; H, 3.0. $C_{20}H_{18}Br_4O_2$ requires C, 39.4; H, 3.0%); $[a]_D^{25}$ +45.3 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1690 (C=C) and 1610 (C=C); δ_H 7.37–7.26 (10H, m, aromatic H), 6.60 (2H, d, *J* 7.32, 2-H and 5-H), 4.68, 4.43 (4H, AB-q, *J* 12.2, benzylic H) and 4.15 (2H, d, *J* 7.3, 3-H and 4-H); δ_C 137.3, 136.0, 128.4, 128.0, 127.9, 92.8, 79.9 and 71.6; *m*/*z* 606 (M$^+$, 0.9%), 607 (4.1), 529 (15), 527 (4.9), 305 (48), 195 (36), 115 (66) and 91 (100).

(3*S*,4*S*)-3,4-Bis(benzyloxy)hexa-1,5-diyne (+)-13

To a solution of **15** (3.80 g, 6.24 mmol) in dry Et_2O (21 cm^3) was added *n*-BuLi in hexane (1.63 mol dm^{-3}; 16.1 cm^3, 26.2 mmol) at −78 °C and the reaction mixture was stirred for 30 min, quenched by addition of saturated aq. NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (50:1) afforded (+)-**13** (1.23 g, 68%) as a colorless oil (Found: C, 82.8; H, 6.3. $C_{20}H_{18}O_2$ requires C, 82.7; H, 6.25%); $[a]_D^{27}$ +134.8 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} 3300 (C≡C–H) and 2100 (C≡C); δ_H 7.35–7.32 (10H, m, aromatic H), 4.85, 4.62 (4H, AB-q, *J* 11.7, benzylic H), 4.31 (2H, s, 3-H and 4-H) and 2.57 (2H, s, 1-H and 6-H); δ_C 137.1, 128.3, 128.0, 127.8, 79.2, 75.8, 70.9 and 70.5; *m*/*z* 290 (M$^+$, 0.7%), 199 (86), 107 (75), 91 (100) and 65 (81).

(1*R*,2*R*,3*R*,4*R*,8*S*,9*S*)-8,9-Bis(benzyloxy)-2,3-(isopropylidenedioxy)cyclododeca-6,10-diyne-1,4-diol (+)-17

According to the procedure described for the preparation of **12**, the diyne derivative **13** (823 mg, 2.84 mmol) in THF (70 cm^3) was successively treated with a solution of *n*-BuLi in hexane (1.46 mol dm^{-3}; 5.83 cm^3, 8.51 mmol) and BF_3·OEt_2 (1.07 cm^3, 8.51 mmol) at −78 °C. A solution of **16** (528 mg, 2.84 mmol) in THF (10.0 cm^3) was added to the borane reagent in THF and the mixture was stirred for 1 h, quenched by addition of saturated aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt gave (+)-**17** (408 mg, 30%) as a colorless oil (Found: M$^+$, 476.2192. $C_{29}H_{32}O_6$ requires *M*, 476.2199); $[a]_D^{26}$ +84.3 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} 3525 (OH) and 2220 (C≡C); δ_H 7.37–7.23 (10H, m, aromatic H), 4.78, 4.59 (4H, AB-q, *J* 11.7, benzylic H), 4.46 (2H, d, *J* 2.9, 2-H and 3-H), 4.37 (2H, s, 8-H and 9-H), 3.93 (2H, m, 1-H and 4-H), 2.78 (2H, dd, *J* 17.1 and 6.8, 5-H and 12-H), 2.64 (2H, d, *J* 17.1, 5-H and 12-H), 2.44 (2H, br s, OH) and 1.41 (6H, s, Me); δ_C 137.4, 128.3, 127.9, 127.7, 108.9, 84.6, 80.6, 78.4, 72.7, 71.2, 70.0, 27.0, 23.5; *m*/*z* 476 (M$^+$, 2.3%), 461 (21), 385 (17), 91 (100), 65 (26) and 59 (31).

(1*R*,2*S*,3*S*,4*R*,8*S*,9*S*)-1,4-Bis(benzoyloxy)-8,9-bis(benzyloxy)-2,3-(isopropylidenedioxy)cyclododeca-6,10-diyne (+)-18

To a solution of **17** (66.0 mg, 0.14 mmol) and Et_3N (87.0 mg, 0.83 mmol) in CH_2Cl_2 (2.0 cm^3) was added a solution of benzoyl chloride (85.0 mg, 0.55 mmol) at 0 °C. The reaction mixture was stirred for 18 h at rt, quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (8:1) to give (+)-**18** (61.5 mg, 66%) as a colorless solid, mp 54–56 °C (from EtOH) (Found: C, 75.3; H, 5.9. $C_{43}H_{40}O_8$ requires C, 75.4; H, 5.9%); $[a]_D^{26}$ +29.0 (*c* 0.26, $CHCl_3$); ν_{max}/cm^{-1} 2250 (C≡C), 1719 (CO); δ_H 8.10 (4H, d, *J* 7.3, aromatic H), 7.54 (2H, t, *J* 7.3, aromatic H), 7.42–7.26 (14H, m, aromatic H), 5.35 (2H, m, 1-H and 4-H), 4.90 (2H, m, 2-H and 3-H), 4.75, 4.56 (4H, AB-q, *J* 11.7, benzylic H), 4.38 (2H, s, 8-H and 9-H), 3.09 (2H, m, 5-H and 12-H), 2.71 (2H, d, *J* 17.1, 5-H and 12-H) and 1.47 (6H, s, Me); δ_C 165.3, 137.3, 133.2, 129.8, 129.5, 128.4, 128.2, 127.8, 127.6,

110.2, 83.6, 79.8, 72.4, 72.0, 70.9, 70.9, 27.2 and 20.9; *m*/*z* 684 (M^+, 0.6%), 669 (4.7), 535 (5.9), 507 (5.1), 456 (5.5), 291 (5.2), 105 (100), 91 (95) and 77 (22).

(1*R*,2*S*,3*S*,4*R*,8*S*,9*S*)-1,4-Bis(benzoyloxy)-8,9-bis(benzyloxy)-cyclododeca-6,10-diyne-2,3-diol (+)-19

A solution of **18** (83.0 mg, 0.12 mmol) in MeOH (2.0 cm^3) and THF (2.00 cm^3) in the presence of conc. HCl (1.0 cm^3) was stirred for 24 h at rt and the solvent was evaporated off. The residue was taken up in AcOEt, which was washed with 10% aq. NaOH, water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2:1) to give (+)-**19** (55.0 mg, 70%) as a colorless solid, mp 46–47 °C (from hexane–AcOEt) (Found: C, 74.2; H, 5.6. $C_{40}H_{36}O_8$ requires C, 74.5; H, 5.6%); $[a]_D^{25}$ +12.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3525 (OH), 2220 (C≡C) and 1719 (CO); δ_H 8.07–8.05 (4H, m, aromatic H), 7.54 (2H, m, aromatic H), 7.39–7.27 (14H, m, aromatic H), 5.25 (2H, m, 1H and 4-H), 4.80 (2H, m, 2-H and 3-H), 4.77, 4.56 (4H, AB-q, *J* 11.7, benzylic H), 4.36 (2H, s, 8-H and 9-H), 3.16 (2H, d, *J* 6.8, OH), 3.02 (2H, dd, *J* 17.6 and 5.9, 5-H and 12-H) and 2.82 (2H, m, 5-H and 12-H); δ_C 166.0, 137.3, 133.4, 129.7, 129.6, 128.6, 128.4, 127.9, 127.8, 83.4, 80.1, 73.7, 72.2, 71.0, 69.2 and 21.8; *m*/*z* 644 (M^+, 0.8%), 614 (0.8), 535 (7.4), 307 (14), 105 (100), 91 (100) and 77 (52).

(1*R*,2*S*,3*S*,4*R*,8*S*,9*S*)-1,4-Bis(benzoyloxy)-2,3-bis[(trimethylsilylethoxymethyl)oxy]-8,9-bis(benzyloxy)cyclododeca-6,10-diyne (+)-20

SEMCl (179 mg, 1.06 mmol) was added to a solution of **19** (68.0 mg, 0.11 mmol) and DIPEA (196 mg, 2.12 mmol) in CH_2Cl_2 (1.0 cm^3) at rt. After being refluxed for 5 h, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (13:1) afforded (+)-**20** (75.0 mg, 79%) as a colorless oil (Found: C, 68.8; H, 7.3. $C_{52}H_{64}O_{10}Si_2$ requires C, 69.0; H, 7.1%); $[a]_D^{27}$ +60.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 2230 (C≡C) and 1719 (CO); δ_H 8.06–7.26 (20H, m, aromatic H), 5.45 (2H, m, 1-H and 4-H), 4.87, 4.85 (4H, AB-q, *J* 6.8, OCH_2O), 4.80, 4.59 (4H, AB-q, *J* 11.7, benzylic H), 4.67 (2H, m, 2-H and 3-H), 4.41 (2H, s, 8-H and 9-H), 3.71–3.55 (4H, m, $TMSCH_2CH_2$), 2.99 (2H, dd, *J* 17.1 and 6.8, 5-H and 12-H), 2.86 (2H, d, *J* 17.1, 5-H and 12-H), 0.89–0.85 (4H, m, $TMSCH_2CH_2$) and −0.05 (18H, s, Me); δ_C 165.5, 137.5, 133.1, 129.9, 129.8, 128.4, 128.3, 127.9, 127.7, 96.4, 83.9, 79.9, 76.0, 72.8, 72.5, 70.9, 66.2, 21.2, 17.9 and −1.5; FABMS *m*/*z* 927 (M^+ + 23, 0.6%), 105 (50), 91 (52), 73 (100) and 55 (17).

(1*R*,2*R*,3*R*,4*R*,8*S*,9*S*)-2,3-Bis[(trimethylsilylethoxymethyl)-oxy]-8,9-bis(benzyloxy)cyclododeca-6,10-diyne-1,4-diol (+)-21

K_2CO_3 (34.0 mg, 0.25 mmol) was added to a solution of **20** (56.0 mg, 0.06 mmol) in MeOH (4.0 cm^3) and the mixture was stirred at rt for 12 h. MeOH was evaporated off and the residue was taken up in AcOEt, which was washed with saturated aq. NH_4Cl, water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (4:1) afforded (+)-**21** (38.0 mg, 87%) as a colorless oil (Found: C, 65.2; H, 8.2. $C_{38}H_{56}O_8Si_2$ requires C, 65.5; H, 8.1%); $[a]_D^{27}$ +10.2 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} 3523 (OH) and 2220 (C≡C); δ_H 7.37–7.26 (10H, m, aromatic H), 4.94, 4.79 (4H, AB-q, *J* 6.8, OCH_2O), 4.76, 4.59 (4H, AB-q, *J* 12.2, benzylic H), 4.43 (2H, d, *J* 3.9, 2-H and 3-H), 4.36 (2H, s, 8-H and 9-H), 4.26 (2H, m, 1-H and 4-H), 3.75–3.69 (4H, m, $TMSCH_2CH_2$), 3.52 (2H, d, *J* 7.8, OH), 2.80 (2H, dd, *J* 16.6 and 5.4, 5-H and 12-H), 2.56 (2H, dd, *J* 16.6 and 9.8, 5-H and 12-H), 0.98–0.94 (4H, m, $TMSCH_2CH_2$) and 0.02 (18H, s, Me); δ_C 137.5, 128.3, 127.8, 127.7, 93.9, 83.3, 79.7, 72.9, 71.3, 69.1, 66.8, 24.2, 18.1 and −1.4; *m*/*z* 696 (M^+, 1.2%), 548 (6.0), 429 (12), 91 (100) and 73 (100).

(1*R*,2*R*,3*S*,4*R*,8*S*,9*S*)-4-Triethylsiloxy-2,3-bis[(trimethylsilyl-ethoxymethyl)oxy]-8,9-bis(benzyloxy)cyclododeca-6,10-diyn-1-ol (+)-22

TESCl (6.20 mg, 0.04 mmol) was added to a solution of **21** (21.0 mg, 0.03 mmol) and imidazole (10.0 mg, 0.15 mmol) in CH_2Cl_2 (0.5 cm^3) and the mixture was stirred at rt for 7 h, quenched by addition of water and diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt afforded (+)-**22** (9.30 mg, 38%) and recovery of the starting material **21** (11.0 mg, 52%). Compound (+)-**22** was obtained as a colorless oil (Found: M^+ + 23, 833.4279. $C_{44}H_{70}O_8Si_3Na$ requires *M* + 23, 833.4276); $[a]_D^{26}$ +82.7 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} 3520 (OH) and 2220 (C≡C); δ_H 7.36–7.25 (10H, m, aromatic H), 4.89–4.56 (8H, m, benzylic H and OCH_2O), 4.45 (1H, m, 2-H), 4.34 (2H, s, 8-H and 9-H), 4.16 (1H, m, 1-H), 4.01 (1H, m, 4-H), 3.96 (1H, dd, *J* 7.3 and 4.4, 3-H), 3.80–3.54 (4H, m, $TMSCH_2CH_2$), 3.46 (1H, m, OH), 2.76–2.54 (4H, m, 5-H and 12-H), 0.98 (9H, t, *J* 7.8, Me), 0.98–0.93 (4H, m, $TMSCH_2CH_2$), 0.64 (6H, q, *J* 7.8, $MeCH_2$), 0.02 (9H, s, Me) and 0.01 (9H, s, Me); δ_C 137.7, 137.6, 128.3, 128.0, 127.9, 127.6, 96.8, 96.7, 85.3, 85.1, 79.7, 79.6, 76.8, 76.3, 72.7, 72.5, 72.2, 70.9, 70.9, 70.6, 66.3, 66.1, 24.9, 23.4, 18.2, 18.1, 6.8, 4.9, −1.4 and −1.5; FABMS *m*/*z* 833 (M^+ + 23, 0.3%), 226 (4.8), 91 (48) and 73 (100).

(2*S*,3*S*,4*R*,8*S*,9*S*)-4-Triethylsiloxy-2,3-bis[(trimethylsilyl-ethoxymethyl)oxy]-8,9-bis(benzyloxy)cyclododeca-10,11-dien-6-yn-1-one (+)-23

A solution of DMSO (76.0 mg, 1.02 mmol) in CH_2Cl_2 (0.5 cm^3) was gradually added to a solution of $(CF_3CO)_2O$ (104 mg, 0.51 mmol) in CH_2Cl_2 (0.5 cm^3) at −78 °C. After stirring of the CH_2Cl_2 solution for 15 min, a solution of the alcohol **22** (81.0 mg, 0.10 mmol) in CH_2Cl_2 (0.5 cm^3) was added and the reaction mixture was stirred at the same temperature for 1 h. Et_3N (152 mg, 1.53 mmol) was added to the reaction mixture, which was then gradually warmed to rt and quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (20:1) afforded (+)-**23** (65.0 mg, 81%) as a colorless oil (Found: M^+ + 23, 831.4113. $C_{44}H_{68}O_8Si_3Na$ requires *M* + 23, 831.4120); $[a]_D^{23}$ +73.4 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} 2230 (C≡C), 1952 (=C=) and 1675 (CO); δ_H 7.37–7.27 (10H, m, aromatic H), 5.97 (1H, dd, *J* 6.3 and 3.3, 12-H), 5.91 (1H, dd, *J* 6.3 and 4.6, 10-H), 5.11 (1H, d, *J* 7.9, 2-H), 4.87–4.48 (9H, m, 3-H, benzylic H and OCH_2O), 4.38 (1H, d, *J* 5.9, 8-H), 4.32 (1H, m, 4-H), 4.23 (1H, m, 9-H), 3.73–3.46 (4H, m, $TMSCH_2CH_2$), 2.90 (1H, m, 5-H), 2.38 (1H, m, 5-H), 0.96 (9H, t, *J* 7.6, Me), 0.96–0.79 (4H, m, $TMSCH_2CH_2$), 0.60 (6H, q, *J* 7.6, CH_2Me), 0.00 (9H, s, Me) and −0.02 (9H, s, Me); δ_C 213.6, 197.6, 137.6, 175.5, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 99.0, 96.5, 95.8, 95.3, 85.6, 81.3, 78.7, 76.3, 75.8, 72.0, 71.4, 70.7, 70.6, 65.6, 65.4, 22.8, 18.0, 17.9, 6.8, 4.7, −1.4 and −1.5; FABMS *m*/*z* 831 (M^+ + 23, 2.4%), 226 (6.8), 91 (84), 87 (24), 73 (100) and 59 (17).

(3*S*,4*S*)-6-(*tert*-Butyldimethylsiloxy)-3,4-bis(methoxy)hexan-1-ol (−)-27

A solution of **26** (1.99 g, 11.4 mmol) in THF (10.0 cm^3) was added to a suspension of NaH (303 mg, 12.6 mmol) in THF (30.0 cm^3) at 0 °C. The THF solution was stirred for 1 h, to which a solution of TBDMSCl (1.90 g, 12.6 mmol) in THF (10.0 ml) was added. After stirring for 3 h, the reaction mixture

was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (5:1) afforded (−)-**27** (2.34 g, 71%) as a colorless oil (Found: C, 57.7; H, 10.9. $C_{14}H_{32}O_4Si$ requires C, 57.5; H, 11.0%); $[a]_D^{26}$ −46.6 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3450 (OH); δ_H 3.76–3.43 (6H, m, 1-H, 3-H, 4-H and 6-H), 3.42 (6H, s, Me), 2.70 (1H, br s, OH), 1.82–1.53 (4H, m, 2-H and 5-H), 0.89 (9H, s, ^{t}Bu), 0.05 (3H, s, Me) and 0.04 (3H, s, Me); δ_C 81.0, 77.5, 61.0, 59.4, 58.5, 58.0, 32.7, 32.1, 25.9, 18.2, −5.4 and −5.4; CIMS *m*/*z* 293 (M^+ + 1, 100), 261 (18), 203 (25), 161 (24) and 89 (84).

(3*S*,4*S*,6*R*,9*S*,10*S*)- and (3*S*,4*S*,6*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-1-(*tert*-butyldimethysiloxy)-3,4-dimethoxydodeca-7,11-diyn-6-ol 28

A solution of DMSO (470 mg, 5.97 mmol) in CH_2Cl_2 (1.0 cm^3) was gradually added to a solution of oxalyl chloride (378 mg, 2.99 mmol) in CH_2Cl_2 (8.0 cm^3) at −78 °C. After stirring of the CH_2Cl_2 solution for 15 min, a solution of the alcohol **27** (291 mg, 1.00 mmol) in CH_2Cl_2 (2.0 cm^3) was added and the reaction was stirred at −78 °C for 1 h. Et_3N (91.0 mg, 8.96 mmol) was added to the reaction mixture, which was then gradually warmed to rt and quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to leave the crude aldehyde. A solution of diyne **13** (866 mg, 2.99 mmol) in THF (2.0 cm^3) was added to a suspension of anhydrous $CeCl_3$ (1.96 g, 7.97 mmol) in THF (25.0 cm^3). The mixture was stirred for 5 min, then LHMDS (0.95 mol dm^{-3}; 6.29 cm^3, 5.97 mmol) was added to the mixture, and the stirring was continued for 1 h at −78 °C. A solution of the crude aldehyde, prepared from **27**, in THF (3.0 cm^3) was then added to the solution of cerium acetylide in THF. The reaction mixture was stirred for 1 h, quenched by addition of saturated aq. NH_4Cl and filtered through Celite. The filtrate was diluted with AcOEt, which was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (4:1) afforded **28** (380 mg, 65%) as a colorless oil (Found: C, 70.0; H, 8.5. $C_{34}H_{48}O_6Si$ requires C, 70.3; H, 8.3%); ν_{max}/cm^{-1} 3460 (OH), 3306 (C≡C–H) and 2120 (C≡C); δ_H 7.39–7.26 (10H, m, aromatic H), 4.84–4.81 (2H, m, benzylic H), 4.69–4.66 (1H, m, 6-H), 4.64–4.59 (2H, m, benzylic H), 4.38 (1H, dd, *J* 6.3 and 1.5, 9-H), 4.31 (1H, dd, *J* 6.3 and 2.4, 10-H), 3.96–3.54 (4H, m, 1-H, 3-H and 4-H), 3.45 ($\frac{59}{100}$ × 3H, s, Me), 3.39 ($\frac{41}{100}$ × 3H, s, Me), 3.39 ($\frac{41}{100}$ × 3H, s, Me), 3.38 ($\frac{59}{100}$ × 3H, s, Me), 2.55 ($\frac{41}{100}$ × 1H, d, *J* 2.4, 12-H), 2.54 ($\frac{59}{100}$ × 1H, d, *J* 2.4, 12-H), 2.01–1.45 (4H, m, 2-H and 5-H), 0.90 (9H, s, ^{t}Bu), 0.06 (3H, s, Me) and 0.06 (3H, s, Me); *m*/*z* 580 (M^+, 0.2), 491 (8.5), 145 (48), 91 (89), 89 (100) and 73 (32).

(3*S*,4*S*,6*R*,9*S*,10*S*)- and (3*S*,4*S*,6*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-1-(*tert*-butyldimethylsiloxy)-3,4-dimethoxy-6-(pivaloyloxy)-dodeca-7,11-diyne 29

PivCl (137 mg, 1.12 mmol) was added to a solution of **28** (325 mg, 0.56 mmol), Et_3N (166 mg, 1.68 mmol) and DMAP (10.0 mg, 0.08 mmol) in CH_2Cl_2 (6.0 cm^3) at 0 °C. After being stirred for 4.5 h at rt, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (13:1) afforded **29** (308 mg, 83%) as a colorless oil (Found: M^+, 664.3796. $C_{39}H_{56}O_7Si$ requires *M*, 664.3795); ν_{max}/cm^{-1} 3306 (C≡C–H), 2120 (C≡C) and 1727 (CO); δ_H 7.36–7.28 (10H, m, aromatic H), 5.63–5.57 (1H, m, 6-H), 4.83–4.77 (2H, m, benzylic H), 4.62–4.57 (2H, m, benzylic H), 4.36 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 4.33 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 4.31 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 2.4, 10-H), 4.28 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 2.4, 10-H), 3.71 (2H, dt, *J* 7.8 and 4.9, 1-H), 3.65–3.49 (2H, m, 3-H and 4-H), 3.40 ($\frac{59}{100}$ × 3H, s, Me), 3.40 ($\frac{41}{100}$ × 3H, s, Me), 3.36 ($\frac{41}{100}$ × 3H, s, Me), 3.36 ($\frac{59}{100}$ × 3H, s, Me), 2.53 ($\frac{41}{100}$ × 1H, d, *J* 2.4, 12-H), 2.51 ($\frac{59}{100}$ × 1H, d, *J* 2.4, 12-H), 2.12–1.49 (4H, m, 2-H and 5-H), 1.24 ($\frac{59}{100}$ × 9H, s, ^{t}Bu), 1.21 ($\frac{41}{100}$ × 9H, s, ^{t}Bu), 0.90 ($\frac{59}{100}$ × 9H, s, ^{t}Bu), 0.90 ($\frac{41}{100}$ × 9H, s, ^{t}Bu), 0.06 ($\frac{59}{100}$ × 3H, s, Me), 0.06 ($\frac{59}{100}$ × 3H, s, Me), 0.06 ($\frac{41}{100}$ × 3H, s, Me) and 0.05 ($\frac{41}{100}$ × 3H, s, Me); *m*/*z* 664 (M^+, 1.1%), 607 (5.5), 519 (13), 461 (11), 145 (35), 91 (100), 89 (57) and 57 (60).

(3*S*,4*S*,6*R*,9*S*,10*S*)- and (3*S*,4*S*,6*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-3,4-dimethoxy-6-(pivaloyloxy)dodeca-7,11-diyn-1-ol 30

To a solution of **29** (308 mg, 0.46 mmol) in THF (2.0 cm^3) was added 75% aq. AcOH (8 cm^3) at rt. The reaction mixture was stirred for 24 h at rt, and quenched by addition of 10% aq. NaOH and extracted with AcOEt. The extract was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2:1) to give **30** (229 mg, 90%) as a colorless oil (Found: M^+, 550.2933. $C_{33}H_{42}O_7$ requires *M*, 550.2931); ν_{max}/cm^{-1} 3470 (OH), 3306 (C≡C–H), 2120 (C≡C) and 1728 (CO); δ_H 7.36–7.26 (10H, m, aromatic H), 5.63–5.58 (1H, m, 6-H), 4.82–4.78 (2H, m, benzylic H), 4.62–4.57 (2H, m, benzylic H), 4.36 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 4.33 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 4.31 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 2.0, 10-H), 4.29 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 2.0, 10-H), 3.79–3.71 (2H, m, 1-H), 3.71–3.49 (2H, m, 3-H and 4-H), 3.43 ($\frac{59}{100}$ × 3H, s, Me), 3.42 ($\frac{41}{100}$ × 3H, s, Me), 3.38 ($\frac{41}{100}$ × 3H, s, Me), 3.37 ($\frac{59}{100}$ × 3H, s, Me), 2.54 ($\frac{59}{100}$ × 1H, d, *J* 2.0, 12-H), 2.53 ($\frac{41}{100}$ × 1H, d, *J* 2.0, 12-H), 2.47 ($\frac{59}{100}$ × 1H, br s, OH), 2.46 ($\frac{41}{100}$ × 1H, br s, OH), 2.14–1.63 (4H, m, 2-H and 5-H), 1.24 ($\frac{41}{100}$ × 9H, s, ^{t}Bu) and 1.21 ($\frac{59}{100}$ × 9H, s, ^{t}Bu); *m*/*z* 550 (M^+, 0.7%), 461 (51), 405 (48), 91 (83) and 57 (100).

(3*S*,4*S*,6*R*,9*S*,10*S*)- and (3*S*,4*S*,6*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-12-iodo-3,4-dimethoxy-6-(pivaloyloxy)dodeca-7,11-diyn-1-ol 31

To a solution of **30** (9.70 mg, 17.6×10^{-3} mmol) in DMF (0.3 cm^3) was successively added NIS (12.0 mg, 52.8×10^{-3} mmol) and $AgNO_3$ (3.00 mg, 17.6×10^{-3} mmol) at rt. The reaction mixture was stirred at rt for 3.5 h and cooled down to 0 °C. Cold water was added to the reaction mixture, which was then extracted with ether several times. The combined layers were washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (2:1) to give **31** (10.5 mg, 88%) as a pale yellow oil (Found: M^+ + 23, 699.1754. $C_{33}H_{41}IO_7Na$ requires *M* + 23, 699.1795); ν_{max}/cm^{-1} 3470 (OH), 2200 (C≡C) and 1728 (CO); δ_H 7.36–7.27 (10H, m, aromatic H), 5.62–5.59 (1H, m, 6-H), 4.81–4.76 (2H, m, benzylic H), 4.61–4.56 (2H, m, benzylic H), 4.42 ($\frac{59}{100}$ × 1H, d, *J* 6.4, 10-H), 4.40 ($\frac{41}{100}$ × 1H, d, *J* 6.4, 10-H), 4.32 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 4.30 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 1.5, 9-H), 3.77–3.73 (2H, m, 1-H), 3.68–3.44 (2H, m, 3-H and 4-H), 3.45 ($\frac{59}{100}$ × 3H, s, Me), 3.43 ($\frac{41}{100}$ × 3H, s, Me), 3.39 ($\frac{41}{100}$ × 3H, s, Me), 3.39 ($\frac{59}{100}$ × 3H, s, Me), 2.55–2.40 (1H, br s, OH), 2.16–1.68 (4H, m, 2-H and 5-H), 1.25 ($\frac{41}{100}$ × 9H, s, ^{t}Bu) and 1.22 ($\frac{59}{100}$ × 9H, s, ^{t}Bu); FABMS *m*/*z* 699 (M^+ + 23, 2.5%), 101 (22), 91 (100) and 57 (44).

(3*S*,4*S*,6*R*,9*S*,10*S*)- and (3*S*,4*S*,6*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-12-iodo-3,4-dimethoxy-6-(pivaloyloxy)dodeca-7,11-diynal 32

PCC (6.50 mg, 30.1×10^{-3} mmol) and MS 4 Å (50.0 mg) was added in one portion to a stirred solution of **31** (5.10 mg, 7.53×10^{-3} mmol) in CH_2Cl_2 (1.0 cm^3) at rt. After being stirred for 3 h, the reaction mixture was filtered through Florisil and washed with ether several times. The filtrate was concentrated to leave the residue which was chromatographed with hexane–AcOEt (4:1) to give **31** (4.70 mg, 93%) as a pale yellow oil (Found: M^+ + 23, 697.1644. $C_{33}H_{39}IO_7Na$ requires *M* + 23,

697.1638); ν_{max}/cm^{-1} 2200 (C≡C) and 1728 (CO); δ_H 9.81 (1H, dd, *J* 3.9 and 1.0, CHO), 7.36–7.26 (10H, m, aromatic H), 5.61–5.58 (1H, m, 6-H), 4.81–4.77 (2H, m, benzylic H), 4.61–4.56 (2H, m, benzylic H), 4.42 ($\frac{59}{100}$ × 1H, d, *J* 6.4, 10-H), 4.40 ($\frac{41}{100}$ × 1H, d, *J* 6.4, 10-H), 4.32 ($\frac{59}{100}$ × 1H, dd, *J* 6.4 and 2.0, 9-H), 4.30 ($\frac{41}{100}$ × 1H, dd, *J* 6.4 and 2.0, 9-H), 3.96–3.44 (2H, m, 3-H and 4-H), 3.40 ($\frac{59}{100}$ × 3H, s, Me), 3.40 ($\frac{41}{100}$ × 3H, s, Me), 3.37 ($\frac{59}{100}$ × 3H, s, Me), 3.35 ($\frac{41}{100}$ × 3H, s, Me), 2.69–2.51 (2H, m, 2-H), 2.17–1.85 (2H, m, 5-H), 1.25 ($\frac{41}{100}$ × 9H, s, ^{t}Bu) and 1.23 ($\frac{59}{100}$ × 9H, s, ^{t}Bu); FABMS *m*/*z* 697 (M^+ + 23, 1.3%), 136 (12), 91 (100) and 57 (58).

$CrCl_2$-mediated coupling reaction of 32

A solution of **32** (77.5 mg, 0.12 mmol) in THF (15 cm^3) was added over a period of 15 min to a suspension of $CrCl_2$ (141 mg, 1.15 mmol) and $NiCl_2$ (7.40 mg, 57 × 10^{-3} mmol) in THF (100 cm^3) at rt. The mixture was stirred for 24 h at rt, diluted with ether which was washed with water and brine, dried and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (3:1) to give (3*S*,4*S*,9*S*,10*S*)-9,10-bis-(benzyloxy)-3,4-dimethoxy-6-(pivaloyloxy)cylcododeca-7,11-diyn-1-ol (**33**) (34.1 mg, 54%) as a mixture of stereoisomers. Compound **33** was a colorless oil (Found: M^+, 548.2778. $C_{33}H_{40}O_7$ requires *M*, 548.2774); ν_{max}/cm^{-1} 3610 (OH), 3420 (OH) and 1728 (CO); δ_H 7.37–7.26 (10H, m, aromatic H), 5.53–5.63 (1H, m, 6-H), 4.79–4.74 (2H, m, benzylic H), 4.70–4.66 (1H, m, 1-H), 4.63–4.55 (2H, m, benzylic H), 4.40–4.34 (2H, m, 9-H and 10-H), 3.92–3.58 (2H, m, 3-H and 4-H), 3.45–3.41 (6H, m, Me), 2.50–2.35 (1H, m, OH), 2.28–1.89 (4H, m, 2-H and 5-H) and 1.24 (9H, s, ^{t}Bu); *m*/*z* 548 (M^+, 0.4%), 153 (3.4), 91 (100), 77 (6.7) and 57 (20).

Reaction of 33 with DIBAL-H

A solution of DIBAL-H in hexane (0.95 mol dm^{-3}; 0.04 cm^3, 41.6 × 10^{-3} mmol) was added to a solution of **33** (5.70 mg, 10.3 × 10^{-3} mmol) in CH_2Cl_2 (1.0 cm^3) at −78 °C. The mixture was stirred for 5 min, quenched by addition of saturated aq. Na_2SO_4 and filtered through Celite. The filtrate was concentrated to leave the residue, which was chromatographed with hexane–AcOEt (1:3) to give (3*S*,4*S*,9*S*,10*S*)-9,10-bis(benzyloxy)-3,4-dimethoxycyclododeca-7,11-diyne-1,6-diol (**34**) (4.50 mg, 94%) as a mixture of stereoisomers. Compound **34** was a colorless oil (Found: M^+, 464.2201. $C_{28}H_{32}O_6$ requires *M*, 464.2199); ν_{max}/cm^{-1} 3610 (OH) and 3431 (OH); δ_H 7.36–7.26 (10H, m, aromatic H), 4.80–4.75 (2H, m, benzylic H), 4.69–4.65 (1H, m, 1-H and 6-H), 4.63–4.58 (2H, m, benzylic H), 4.44–4.35 (1H, m, 9-H and 10-H), 4.08–3.66 (2H, m, 3-H and 4-H), 3.48–3.43 (6H, m, Me) and 2.24–1.95 (4H, m, 2-H and 5-H); *m*/*z* 464 (M^+, 0.7%), 446 (0.9), 105 (7.9), 91 (100) and 77 (9.7).

(3*S*,4*S*,9*S*,10*S*)-9,10-Bis(benzyloxy)-3,4-dimethoxycyclododeca-7,11-diyne-1,6-dione (+)-35

According to the procedure described for conversion of **31** to **32**, **34** (1.50 mg, 3.23 × 10^{-3} mmol) in CH_2Cl_2 (1.0 cm^3) was oxidized with PCC (11.0 mg, 51.0 × 10^{-3} mmol) in the presence of MS 4 Å (50.0 mg). Work-up gave the residue which was chromatographed with hexane–AcOEt (3:1) to give (+)-**35** (1.20 mg, 81%) as a colorless solid mp 94–95 °C (from hexane–AcOEt) (Found: M^+, 460.1882. $C_{28}H_{28}O_6$ requires *M*, 460.1886); $[\alpha]_D^{25}$ +50.8 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} 2220 (C≡C) and 1672 (CO); δ_H 7.37–7.29 (10H, m, aromatic H), 4.80, 4.60 (4H, AB-q, *J* 11.7, benzylic H), 4.55 (4H, s, 9-H and 10-H), 4.10 (2H, m, 3-H and 4-H), 3.37 (6H, s, Me), 3.03 (2H, dd, *J* 15.6 and 9.3, 2-H and 5-H) and 2.86 (2H, dd, *J* 15.6 and 3.9, 2-H and 5-H); δ_C 184.2, 136.1, 128.6, 128.4, 128.0, 89.5, 85.4, 78.1, 72.1, 71.4, 58.1 and 45.4; *m*/*z* 460 (M^+, 9.3%), 369 (14), 337 (14), 139 (18) and 91 (100).

References

1 N. Ishida, K. Miyazaki, K. Kumagai and M. Rikimaru, *J. Antibiot.*, 1965, **18**, 68.
2 K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Otake and N. Ishida, *Tetrahedron Lett.*, 1985, **26**, 331.
3 K. S. Lam, G. A. Hesler, D. R. Gustavson, A. R. Crosswell, J. M. Veitch, S. Forenza and K. Tomita, *J. Antibiot.*, 1991, **44**, 472.
4 J. Hu, Y.-C. Xue, M.-Y. Xie, Y. Zhang, T. Otani, Y. Minami, Y. Yamada and T. Marunaka, *J. Antibiot.*, 1988, **41**, 1575.
5 M. Hanada, H. Ohkuma, T. Yonemoto, K. Tomita, M. Ohbayashi, H. Kamei, T. Miyaki, M. Konishi, H. Kawaguchi and S. Forenza, *J. Antibiot.*, 1991, **44**, 403.
6 T. Ando, M. Ishii, T. Kajiura, Y. Kameyama, K. Miwa and Y. Sugiura, *Tetrahedron Lett.*, 1998, **39**, 6495.
7 (*a*) P. A. Wender, M. Harmata, D. Jeffrey, C. Mukai and J. Suffert, *Tetrahedron Lett.*, 1988, **29**, 909; (*b*) P. A. Wender, J. A. McKinney and C. Mukai, *J. Am. Chem. Soc.*, 1990, **112**, 5369; (*c*) P. Magnus and M. Davis, *J. Chem. Soc., Chem. Commun.*, 1991, 1522; (*d*) T. Takahashi, H. Tanaka, Y. Hirai, T. Doi, H. Yamada, T. Shiraki and Y. Sugiura, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1657; (*e*) A. G. Myers, M. Hammond, Y. Wu, J.-N. Xiang, P. M. Harrington and E. Y. Kuo, *J. Am. Chem. Soc.*, 1996, **118**, 10006; (*f*) P. Magnus, R. Carter, M. Davis, J. Elliott and T. Pitterna, *Tetrahedron Lett.*, 1996, **37**, 6283; (*g*) S. Caddick and V. M. Delisser, *Tetrahedron Lett.*, 1997, **38**, 2355.
8 (*a*) M. Hirama, K. Fujiwara, K. Shigematu and Y. Fukazawa, *J. Am. Chem. Soc.*, 1989, **111**, 4120; (*b*) M. Hirama, T. Gomibuchi and K. Fujiwara, *J. Am. Chem. Soc.*, 1991, **113**, 9851; (*c*) K. Nakatani, K. Arai and S. Terashima, *J. Chem. Soc., Chem. Commun.*, 1992, 289; (*d*) J. Suffert, E. Abraham, S. Raeppel and R. Brückner, *Liebigs Ann. Chem.*, 1996, 334; (*e*) K. Brickmann, F. Hambloch, J. Suffert and R. Brückner, *Liebigs Ann. Chem.*, 1996, 357; (*f*) M. Eckhardt and R. Brückner, *Liebigs Ann. Chem.*, 1996, 473 and references cited therein.
9 During this investigation, Myers and Goldberg have recently reported a novel transformation reaction of the twelve-membered tetrayne derivative into the corresponding bicyclo[7.3.0]dodecadienediyne: A. G. Myers and S. D. Goldberg, *Tetrahedron Lett.*, 1998, **39**, 9633.
10 For recent reviews on medium-sized cyclic diynes, see (*a*) R. Gleiter and R. Merger, in *Cyclic Alkynes, Preparation and Properties in Modern Acetylene Chemistry*, ed. P. J. Stang and F. Diederich, VCH, Weinheim, 1995, p. 285; (*b*) C. Boss and R. Keese, *Tetrahedron*, 1997, **53**, 3111 and references cited therein.
11 J. Kuszmann, *Carbohydr. Res.*, 1979, **71**, 123.
12 M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.
13 B. B. Lohray, Y. Jayamma and M. Chatterjee, *J. Org. Chem.*, 1995, **60**, 5958.
14 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
15 H. Nemoto, S. Takamatsu and Y. Yamamoto, *J. Org. Chem.*, 1991, **56**, 1321.
16 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, **13**, 3769.
17 Y. L. Merrer, A. Dureault, C. Greck, D. M. Languin, C. Gravier and J.-C. Depezay, *Heterocycles*, 1987, **25**, 541.
18 Numbering for NCS chromophore (**1**) was employed for convenience.
19 The structure of **23** was elucidated by spectral evidence. The IR spectrum showed a diagnostical absorption band at 1952 cm^{-1}, a typical allenic band, along with a carbonyl absorption at 1675 cm^{-1}. In the ^{1}H NMR spectrum, two characteristically lower field-shifted peaks appeared at δ 5.97 (dd, *J* = 6.3 and 3.3 Hz) and 5.91 (dd, *J* = 6.3 and 4.6 Hz) attributable to H-8 [18] and H-6, respectively. The decoupling experiments disclosed that H-5 coupled not only with H-8 (*J* = 3.3 Hz), but also with H-6 (*J* = 4.6 Hz) strongly supporting the structure. Furthermore, a diagnostic peak due to the allenic carbon at δ 213.6 was observed in the ^{13}C NMR spectrum.
20 A similar isomerization from the propargyl (prop-2-ynyl) ketone moiety to the corresponding allenyl ketone functionality was reported: (*a*) G. Majetich, Y. Zhang and G. Dreyer, *Tetrahedron Lett.*, 1993, **34**, 449; (*b*) A. S. K. Hashmi, J. W. Bats, J.-H. Choi and L. Schwarz, *Tetrahedron Lett.*, 1998, **39**, 7491 and references cited therein.
21 A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.*, 1964, **86**, 5626.
22 (*a*) A. G. Myers, P. M. Harrington and E. Y. Kuo, *J. Am. Chem. Soc.*, 1991, **113**, 694; (*b*) K. Iida and M. Hirama, *J. Am. Chem. Soc.*, 1994, **116**, 10310; (*c*) I. Sato, K. Toyama, T. Kikuchi and M. Hirama, *Synlett*, 1998, 1308.
23 (*a*) K. C. Nicolaou, A. Liu, Z. Zeng and S. McComb, *J. Am. Chem. Soc.*, 1992, **114**, 9279; (*b*) C. Meert, J. Wang and P. J. De Clercq, *Tetrahedron Lett.*, 1997, **38**, 2179; (*c*) M. F. Semmelhack, Y. Gu and D. M. Ho, *Tetrahedron Lett.*, 1997, **38**, 5583.

24 T. Nishizawa, S. Shibuya, S. Hosokawa and M. Isobe, *Synlett*, 1994, 485.
25 Several attempts were made to develop a more convenient procedure involving fewer steps for obtaining **34**. For example, the dialdehyde compound derived from **26** (*e.g.*, compound **6** in Scheme 1) was reacted with dicerium acetylide or diiodoacetylene derivatives, prepared from **13**, to afford an intractable mixture.
26 Several preliminary attempts on conversion of **35** into the corresponding bicyclo[7.3.0]dodecadiyne derivatives were made under typical aldol conditions by using LDA or LHMDS. However, no ring closed compounds have so far been isolated from the reaction mixture.

Paper a909089d