A ketal Claisen rearrangement for α-ketol isoprene unit elongation: application to a practical synthesis of sarcophytol A intermediate

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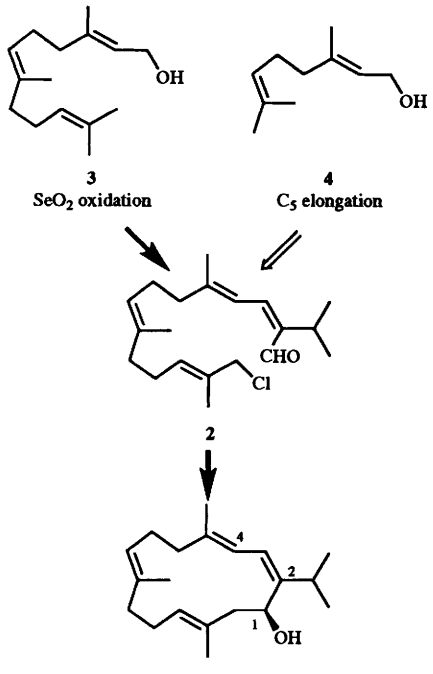
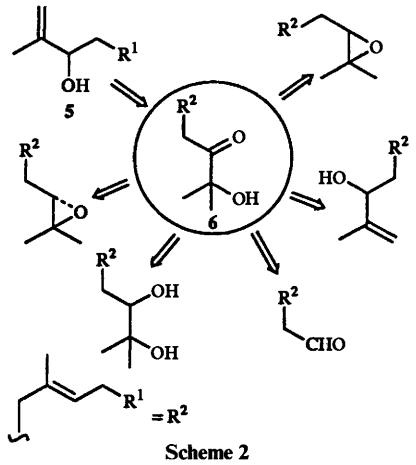
A new ketal Claisen rearrangement using the ketal **10** for the isoprene unit elongation which affords terminal α-ketol terpenoid is presented. Its efficiency is demonstrated by successful transformation of the product of this reaction, the α-ketol **20**, into **2**, the acyclic precursor of sarcophytol A total synthesis, by two alternative routes *via* the β,γ-unsaturated aldehyde **24** and the allylic alcohol **28**.

Sarcophytol A **1**,[1] a cembrane-type diterpene isolated from the soft coral *Sarcophyton glaucum* has been shown to have antitumour activity and also to be a potent inhibitor of antitumour promoters; it is, therefore, a promising cancer chemopreventive agent.[2] The total synthesis of this compound has been achieved by several groups including our own.[3] In our first total synthesis of **1**, of which the key intermediate was the chloro aldehyde **2**, *E,E*-farnesol **3** was used as the starting material (Scheme 1).[2,3a] However, low regioselective SeO_2



Scheme 1

oxidation of the farnesyl carbon framework proved a drawback, necessitating termination of the reaction before completion and laborious chromatography to remove the regioisomer; this resulted in a low yield of product (usually at best only about 50% of consumed starting material). This prompted us to seek a more efficient synthetic route toward **1** starting with geraniol **4**, which required elongation of a functionalized isoprene (C_5) unit. Ketal Claisen rearrangements[4] are prominent methods for C_5 elongation by which a C_5 α,β-unsaturated ketone[5] or α-chloro ketone[6] have been attached highly stereoselectively to a precursor allylic alcohol **5**, and have frequently been utilized in natural product syntheses.[7] The terminal α-ketol **6** of the acyclic terpenoid is a versatile functional group readily convertible into an α-diol, (chiral)epoxide or allylic alcohol, *etc.* (Scheme 2). However, **6** has not been employed much in

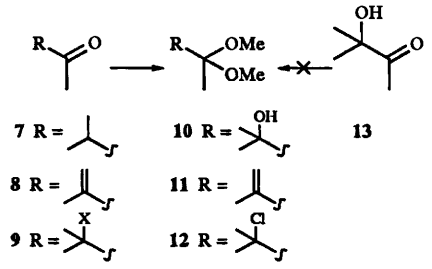


Scheme 2

terpenoid chemistry, presumably because of the lack of a straightforward synthetic method. Herein we report a new ketal Claisen rearrangement for the C_5 unit elongation which affords the α-ketol **6** as the product, and its efficiency is demonstrated by application to the practical synthesis of the key intermediate **2** for a total synthesis of sarcophytol A.

Results and discussion

We chose an isoprene derivative, 2,2-dimethoxy-2,3-dimethylbutan-2-ol **10**, as a vinylating agent for ketal Claisen rearrangement. The ketal **10**, which had not previously been employed in this rearrangement, was readily prepared from 3-methylbutan-2-one **7**, *via* 3-bromo-3-methylbutan-2-one **9** (X = Br)[8] according to the literature.[9] It was difficult to isolate **10** in a pure form by Hg-catalysed addition[10] of methanol to 2-methylbut-3-yn-2-ol. The substrate for ketal Claisen rearrangement, the allylic alcohol **18**, was prepared from geraniol **4** as follows. The (2*Z*,4*E*)-diene moiety was constructed by a *Z*-selective (2*Z*:2*E* = >22:1) Horner–Emmons reaction[11] of geranial **14**, which was obtained from **4** by $BaMnO_4$ oxidation, with the phosphonate nitrile **15** in 90% yield. The terminal double bond of the thus obtained nitrile **16** was selectively oxidized in 97% yield using MPCBA, to give the epoxide **17** which was converted into the allylic alcohol **18** in 98% yield by $Al(OPr^i)_3$ treatment in toluene without affecting its conjugated diene nitrile moiety. The ketal Claisen rearrangement of **18** was performed with 3.5 mol equiv. of **10** at 130 °C for 5 h, 2 mol % of 2,4-dinitrophenol being sufficient as catalyst. The desired 8*E*-olefinic α-ketol **20**

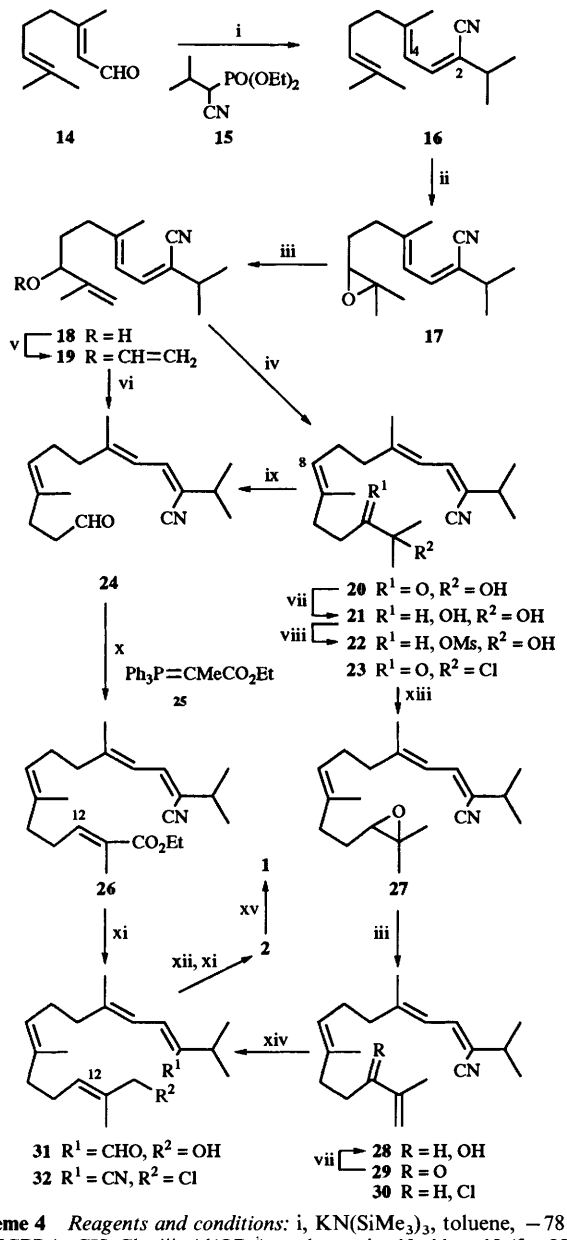


Scheme 3

was obtained highly stereoselectively (>99%) in 91% yield after column chromatographic purification. The *E*:*Z* ratio of the newly formed double bond was determined by capillary GLC analysis of the crude β,γ-unsaturated aldehyde **24** derived from **20** by $NaBH_4$ reduction, and by subsequent oxidative cleavage of the resulting α-diol **21** with $NaIO_4$ without purification in either step. The Claisen rearrangement of the vinyl ether **19** in refluxing toluene was performed in order to identify the *Z*-isomer of **24** by capillary GLC; the *E*-selectivity of this reaction was 89%. The high *E*-selectivity is explained by the presence of the bulky substitutent $-C(Me)_2OH$ arising from **10** in the transition state of the ketal Claisen rearrangement. Moreover, the tertiary carbon in the substituent avoids the regiochemical problem of ketal Claisen rearrangement,[12] and is the probable reason for the high yield. To allow a direct comparison of the present ketal Claisen rearrangement with the previous methods for isoprenyl unit elongation, we also carried out the reactions of **18** using the known ketals, **11**[5] and **12**.[6] The rearranged products, unsaturated ketone **29** and the α-chloro ketone **23**, were obtained in 64 and 70% yield, respectively. Thus, since the present ketal Claisen rearrangement using **10** proceeds more cleanly than known ketal Claisen rearrangements, the following facts are noteworthy. The ketals **11** and **12** were readily prepared by direct ketalization (orthoformate and an excess of methanol in the presence of acid catalyst)[6] of the corresponding α,β-unsaturated ketone **8** and α-chloro ketone **9** (X = Cl), respectively (Scheme 3). Under the same reaction conditions, however, the desired ketalization of **13** failed to proceed. In ketal Claisen rearrangements the rearranged products possess the same parent ketone skeleton as the starting ketal agents, and thus may serve as new vinylating agents after ketalization.

Having developed a method for the efficient construction of α-ketols, we focused our attention on determining the potential synthetic usefulness of the rearranged product employing **20**. The α-ketol **6** has recently been shown to be an excellent substrate for yeast reduction and to give, eventually, an asymmetric epoxyterpenoid.[13] Enantioselective syntheses of both enantiomers of sarcophytols A and T from **20** have been achieved by this methodology.[3c] Since this success, we have continued our effort to convert **20** efficiently into the key intermediate **2**[2,3a] of our sarcophytol A total synthesis with the goal of developing a practical synthetic route for **1**.

First, the aldehyde **24**, which was derived from **18** in 83% overall yield without isolation of the intermediates **20** and **21**, was submitted to Kishi's Wittig reaction conditions (the phosphorane **25** in CH_2Cl_2 at room temperature for 5 h)[14] to give in 97% yield the 12*E*-α,β-unsaturated ester **26** contaminated, as shown by capillary GLC, with 3% of the 12*Z*-isomer, which was readily removable by silica gel (SiO_2) flash column chromatography. Both the ester and nitrile groups in **26** were simultaneously reduced with diisobutylaluminium hydride (DIBAL; 3.5 mol equiv.) at −78 °C, and subsequent careful hydrolysis[3a,11] of the resulting imine with aqueous 1 mol dm^{-3} oxalic acid at 0 °C; this gave the desired hydroxy aldehyde **31** in 79% yield after SiO_2 flash column chromatographic



Scheme 4 *Reagents and conditions:* i, $KN(SiMe_3)_3$, toluene, −78 °C; ii, MCPBA, CH_2Cl_2; iii, $Al(OPr^i)_3$, toluene; iv, **10**, **11** or **12** (for **29**), 2 mol % of 2,4-dinitrophenol, 130 °C; v, $EtOCH{=}CH_2$, $Hg(AcO)_2$; vi, toluene, 110 °C; vii, $NaBH_4$, MeOH; viii, MeCl, Py; ix, $NaIO_4$, $MeOH–H_2O$; x, **25**, CH_2Cl_2; xi, DIBAL, toluene, −78 °C; xii, MsCl, LiCl, DMF; xiii, K_2CO_3, MeOH; xiv, $SOCl_2$, Et_2O; xv, see text

purification. Finally, substitution of the hydroxy group in **31** with chloride was expected to provide the desired compound **2**. Attempted chlorination of **31** with triphenylphosphine in refluxing CCl_4 was unsuccessful, resulting in a complex mixture of geometrical isomers of the dienal moiety. However, upon treatment with methanesulfonyl chloride (MsCl) in the presence of lithium chloride and 2,6-dimethylpyridine in dimethylformamide (DMF), the hydroxy aldehyde **31** produced the chloro aldehyde **2** in 87% yield, without isomerization, which was identical with the previously prepared compound **2**[2,3a] in its chromatographic and spectroscopic properties.

In addition, selective mesylation of the diol **21**, the reduction product of **20**, with MsCl in pyridine (94%) and subsequent K_2CO_3 treatment in methanol (92%) afforded the epoxide **27**. The epoxide ring was opened by the same procedure as that described for the conversion of **17** into **18**, and the allylic alcohol **28** was obtained in 86% yield. It was also possible to obtain the

alcohol **28** from **18** in 71% overall yield using the crude intermediate without purification in each step; this was higher than that (61%) of the same conversion of **18** into **28** by the reaction using the ketal **11** without isolation of the α,β-unsaturated ketone **29**. The next step was S_Ni' chlorination[15] of the allylic alcohol **28**. When **28** was treated as a 0.33 mol dm^{-3} solution in hexane[5b,16] with thionyl chloride, the chloride **32** contaminated with an unexpectedly high 20% (capillary GLC) of the secondary chloride **30** was obtained in 90% yield. SiO_2 column chromatographic separation of **32** and **30** was, unfortunately, difficult. Despite attempts to reduce the formation of the isomeric chloride **30**, *i.e.* reactions under diluted reaction conditions (0.03 mol dm^{-3}) and in diethyl ether[15] instead of hexane, gave **30** in 11 and 7.5% yields, respectively. We were able to confirm, however, that **1** was successfully synthesized, even if **32** contaminated with **30** was used as the starting material. Namely, the mixture of **32** and **30** (**32**:**30** = 4:1) was subjected to a slightly modified five-step sequence[2] as previously reported: (1) DIBAL reduction affording **2**, (2) protected cyanohydrin formation of **2**, (3) macrocyclization, (4) generation of the macrocyclic ketone by deprotection, (5) enantioselective reduction of the ketone with $LiAlH_4$ chirally modified with (1*R*,2*S*)-(−)-*N*-methylephedrine at −20 °C. Purification was not carried out at any step of the sequence except the final step. The desired compound **1** of 89% ee (chiral HPLC) was produced in 40% overall yield, from which enantiomerically pure (>99% ee) compound **1**[2] was obtained as white crystals upon a single recrystallization.

Thus, the α-ketol **20**, the product of the ketal Claisen rearrangement reaction using **10**, was successfully converted into **2**, the acyclic precursor of sarcophytol A total synthesis by two alternative routes: *via* the β,γ-unsaturated aldehyde **24** and allylic alcohol **28**. These overall yields of **2** from geraniol **4** were higher than that of the previous synthesis starting with *E,E*-farnesol **3**. In addition, commercially available **4** is both cheaper and purer than compound **3**.

Experimental

Flash column chromatography was performed on silica gel 60 (Merck) using as eluent hexane–ethyl acetate (ratio of solvents used given in parentheses). TLC was performed on pre-coated plates of silica gel $60F_{254}$ (Merck). IR spectra were recorded on a JASCO IR A-102 spectrometer. ^1H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ on Bruker AC-250 or AMX-500 spectrometers; chemical shifts are reported on the δ scale from internal Me_4Si, and *J* values are given in Hz. All electron-impact mass and HRMS data were measured at 70 eV on a Hitachi M-3000 mass spectrometer. GLC was carried out on a Shimadzu GC-9A gas chromatograph equipped with a capillary column of CBP1, 0.3 mm × 25 m. HPLC was performed on a Shimadzu LC-9A as a pump and a SPD-6A as a detector.

2,2-Dimethoxy-2,3-dimethylbutan-2-ol 10

To a stirred and cooled mixture of 3-methylbutan-2-one (68 cm^3, 0.636 mol) and aluminium chloride (1.6 g, 12 mmol) was added dropwise bromine (16 cm^3, 0.31 mol) at 3–7 °C. The mixture was stirred for a further 30 min, after which it was allowed to rise to room temperature. Ice and water were added to the mixture, and the organic layer was separated, washed with water, dried ($MgSO_4$) and distilled to give 3-bromo-3-methylbutan-2-one **9** (X = Br) (92% purity, determined by GLC; 39.4 g, 73%), bp 50–54 °C/35 mmHg (lit.,[9] 83–84 °C/150 mmHg).

To an ice-cooled, stirred solution of sodium methoxide (28% in methanol; 47 cm^3, 0.23 mol) diluted with methanol (30 cm^3) the foregoing distillate was added dropwise. After being stirred for 30 min at room temperature, the mixture was filtered and the filtrate was concentrated to remove the methanol. Distillation of the residue gave the ketal **10** (98.2% purity, GLC; 21.2 g, 64%), bp 86–88 °C/65 mmHg (lit.,[10a] 159–161 °C/730 mmHg); ν_{max}(neat)/cm^{-1} 3520; δ_H(250 MHz) 1.16 [6 H, s, CMe_2OH), 1.22 (3 H, s, $CMe(OMe)_2$], 2.29 (1 H, br s, OH) and 3.30 (6 H, s, OMe).

(2*Z*,4*E*)-5,9-Dimethyl-2-(1-methylethyl)deca-2,4,8-trienenitrile 16

To a stirred solution of the phosphonate **15** (6.54 g, 30 mmol) in dry THF (55 cm^3) at −78 °C under argon atmosphere was added a toluene solution of potassium bis(trimethylsilyl)amide (0.5 mol dm^{-3}; 56 cm^3). After 30 min, geranial **14** (3.80 g, 25 mmol) was added to the mixture which was then gradually warmed to room temperature overnight with continuous stirring. After addition of water to the mixture the organic layer was separated and the aqueous layer was extracted with diethyl ether (×3). The combined organic layer and extracts were washed with brine, dried ($MgSO_4$) and evaporated to give the crude nitrile as a 22.4:1 mixture of **16** and its (2*E*,4*E*) isomer according to GLC analysis. Compound **16** (4.87 g, 90%) was obtained by flash column chromatography (100:1) as an oil (Found: C, 82.6; H, 10.7; N, 6.3. $C_{15}H_{23}N$ requires C, 82.89; H, 10.67; N, 6.44%); ν_{max}(neat)/cm^{-1} 2220, 1640 and 1450; δ_H(250 MHz) 1.17 (6 H, d, *J* 6.8, $CHMe_2$), 1.61 (3 H, s, 10-H), 1.69 (3 H, s, 9-Me), 1.83 (3 H, d, *J* 1.2, 5-Me), 2.1–2.2 (4 H, m, 6 and 7-H), 2.53 (1 H, sept, *J* 6.8, $CHMe_2$), 5.08 (1 H, m, 8-H), 6.28 (1 H, d, *J* 11.5, 4-H) and 6.82 (1 H, d, *J* 11.5, 3-H); δ_C(62.5 MHz) 17.4 (q), 17.8 (q), 21.7 (q) ×2, 25.7 (q), 26.5 (t), 33.4 (d), 40.3 (t), 117.6 (s), 117.8 (s), 121.9 (d), 123.4 (d), 132.3 (s), 137.7 (s) and 147.9 (s); *m/z* 217 (M^+, 35%), 134 (80) and 69 (100) (Found: M^+, 217.1873. $C_{15}H_{23}N$ requires *M*, 217.1830).

(2*Z*,4*E*)-8,9-Epoxy-5,9-dimethyl-2-(1-methylethyl)deca-2,4-dienenitrile 17

To a stirred solution of the nitrile **16** (2.0 g, 9.2 mmol) in CH_2Cl_2 (40 cm^3) at 0 °C was added portionwise MCPBA (purity 80%; 2.0 g, 9.3 mmol). The mixture was stirred at the same temperature for 1 h and then at room temperature for 3 h. After this, saturated aqueous $NaHCO_3$ was added to the mixture, which was then vigorously stirred for 30 min. The organic layer was then separated and the aqueous layer was extracted with diethyl ether. The combined organic layer and extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was purified by flash column chromatography (10:1) to give the epoxide **17** (2.08 g, 97%) as an oil (Found: C, 77.0; H, 10.2; N, 6.3. $C_{15}H_{23}NO$ requires C, 77.21; H, 9.93; N, 6.00%); ν_{max}(neat)/cm^{-1} 2210, 1640 and 1460; δ_H(250 MHz) 1.17 (6 H, d, *J* 6.8, $CHMe_2$), 1.27 and 1.32 (each 3 H, s, 9-Me), 1.7 (2 H, m, 7-H), 1.86 (3 H, s, 5-Me), 2.2–2.3 (2 H, m, 6-H), 2.54 (1 H, sept, *J* 6.8, $CHMe_2$), 2.72 (1 H, t, *J* 6.8, 8-H), 6.31 (1 H, dd, *J* 0.9, 11.5, 4-H), 6.83 (1 H, d, *J* 11.5, 3-H), 5.08 (1 H, m, 8-H), 6.28 (1 H, d, *J* 11.5, 4-H) and 6.82 (1 H, d, *J* 11.5, 3 H); δ_C(125 MHz) 17.4 (q), 17.8 (q), 21.7 (q) ×2, 25.7 (q), 26.5 (t), 33.4 (d), 40.3 (t), 117.6 (s), 117.8 (s), 121.9 (d), 123.4 (d), 132.3 (s), 137.7 (s) and 147.9 (s); *m/z* 233 (M^+, 1%), 218 (4), 162 (50), 85 (80) and 43 (100).

(2*Z*,4*E*)-8-Hydroxy-5,9-dimethyl-2-(1-methylethyl)deca-2,4,9-trienenitrile 18

To a stirred solution of the epoxide **17** (1.83 g, 7.85 mmol) in dry toluene (16 cm^3) under a nitrogen atmosphere was added $Al(OPr^i)$ (1.60 g, 7.84 mmol). The mixture was heated on a bath at 110 °C for 8 h after which it was cooled to room temperature. The mixture was diluted with hexane (16 cm^3) and shaken well with 2 mol dm^{-3} hydrochloric acid after which the organic layer was separated and the water layer was extracted with diethyl

ether. The combined organic layer and extracts were washed with water and saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (6:1) to give the allylic alcohol **18** (1.80 g, 98%) as an oil, ν_{max}(neat)/cm^{-1} 3450, 2210, 1640 and 1450; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.9, CH*Me*$_2$), 1.60 (1 H, d, OH), 1.71 (2 H, m, 7-H), 1.74 (3 H, s, 9-Me), 1.85 (3 H, s, 5-Me), 2.21 (2 H, m, 6-H), 2.53 (1 H, sept, *J* 6.9, C*H*Me$_2$), 4.06 (1 H, m, 8 H), 4.87 (1 H, s, C=CH$_2$), 4.97 (1 H, s, C=CH$_2$), 6.31 (1 H, d, *J* 11.5, 3-H) and 6.82 (1 H, d, *J* 11.5, 4-H); δ_C(125 MHz) 17.4 (q), 17.6 (q), 21.6 (q) ×2, 32.9 (t), 33.3 (d), 36.2 (t), 75.3 (d), 111.4 (s), 117.5 (s), 117.9 (s), 121.9 (d), 137.5 (s), 147.1 (s) and 147.5 (s); *m*/*z* 217 (M$^+$, 35%), 134 (80) and 69 (100) (Found: M$^+$, 233.1789. $C_{15}H_{23}NO$ requires *M*, 233.1779).

(2*Z*,4*E*,8*E*)-13-Hydroxy-5,9,13-trimethyl-(1-methylethyl)-12-oxotetradeca-2,4,8-trienenitrile 20

A mixture of the allylic alcohol **18** (700 mg, 3.0 mmol), the ketal **10** (1.55 g, 10.5 mmol) and 2,4-dinitrophenol (9 mg, 0.06 mmol) was heated on a 130 °C oil-bath for 5 h under an argon atmosphere while the methanol formed was distilled off. Unchanged compound **10** was evaporated under reduced pressure, and the residue was purified by flash column chromatography (6:1) to give the α-ketol **20** (866 mg, 91%) as an oil (Found: C, 75.4; H, 9.8; N, 4.3. $C_{20}H_{31}NO_2$ requires C, 75.66; H, 9.84; N, 4.41%); ν_{max}(neat)/cm^{-1} 3520, 2220, 1715, 1640 and 1470; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.38 (6 H, s, 13-Me), 1.63 (3 H, s, 9-Me), 1.83 (3 H, s, 5-Me), 2.17 (4 H, m, 6 and 7-H), 2.29 (2 H, t, *J* 7.5, 10-H), 2.53 (1 H, sept, *J* 6.8, C*H*Me$_2$), 2.65 (2 H, t, *J* 7.5, 11-H), 5.12 (1 H, br m, 8-H), 6.26 (1 H, d, *J* 11.5, 4-H) and 6.82 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 16.2 (q), 17.4 (q), 21.6 (q) ×2, 26.1 (t), 26.5 (q) ×2, 33.3 (q), 33.3 (t), 34.4 (t), 39.9 (t), 76.2 (s), 117.6 (s), 117.8 (s), 121.9 (d), 124.1 (d), 134.4 (s), 137.6 (d), 147.4 (s) and 214.1 (s); *m*/*z* 317 (M$^+$, 0.5%), 274 (4), 231 (10), 216 (5), 134 (30), 83 (70) and 59 (100).

(2*Z*,4*E*,8*E*)-2-(5,9,13-Trimethyl-1-methylethyl)-12-oxotetradeca-2,4,8,13-tetraenenitrile 29

A stirred mixture of the alcohol **18** (320 mg, 1.37 mmol), 3,3-dimethoxy-2-methylbutene **11** (895 mg, 6.87 mmol) and 2,4-dinitrophenol (6 mg, 0.04 mmol) was heated at 110 °C for 8 h under an argon atmosphere while the generated methanol was removed. After the reaction mixture had cooled, unchanged compound **11** was evaporated, and the residue was chromatographed (7:1) to give the conjugated ketone **29** (262 mg, 64%) as an oil, ν_{max}(neat)/cm^{-1} 2215, 1680, 1635 and 1450; δ_H(250 MHz) 1.14 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.60 (3 H, s, 9-Me), 1.80 (3 H, s, 5 or 13-Me), 1.84 (3 H, s, 13 or 5-Me), 2.14 (4 H, m, 6 and 7-H), 2.25 (2 H, br t, *J* 7.5, 10-H), 2.50 (1 H, sept, *J* 6.8, C*H*Me$_2$), 2.75 (2 H, t, *J* 7.5, 11-H), 5.08 (1 H, br m, 8-H), 5.75 (1 H, s, C=CH$_2$), 5.95 (1 H, s, C=CH$_2$), 6.24 (1 H, d, *J* 11.5, 4-H) and 6.79 (1 H, d, *J* 11.5, 3-H).

(2*Z*,4*E*,8*E*)-12-Chloro-5,9,13-trimethyl-2-(1-methylethyl)-tetradeca-2,4,8,13-tetraenenitrile 30

A stirred mixture of the alcohol **18** (316 mg, 1.36 mmol), 2-chloro-3,3-dimethoxy-2-methylbutane **12** (550 mg, 4.10 mmol) and 2,4-dinitrophenol (12 mg, 0.065 mmol) was heated at 130 °C on an oil bath for 3 h under argon atmosphere while generated methanol was removed. After the reaction mixture had cooled, unchanged compound **12** was evaporated, and the residue was chromatographed (7:1) to give the conjugated ketone **29** (319 mg, 70%) as an oil; ν_{max}(neat)/cm^{-1} 2220, 1720 and 1640 and 1455; δ_H(250 MHz) 1.14 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.61 (3 H, s, 9-Me), 1.65 (3 H, s, 13-Me), 1.80 (3 H, s, 5-Me), 2.14 (4 H, m, 6 and 7-H), 2.25 (2 H, br t, *J* 7.7, 10-H), 2.50 (1 H, sept, *J* 6.8, C*H*Me$_2$), 2.83 (2 H, t, *J* 7.5, 11-H), 5.11 (1 H, br m, 8-H), 6.25 (1 H, d, *J* 11.5, 4-H) and 6.79 (1 H, d, *J* 11.5, 3-H).

(2*Z*,4*E*,8*E*)-12,13-Dihydroxy-5,9,13-trimethyl-2-(1-methylethyl)tetradeca-2,4,8-trienenitrile 21

To a stirred solution of the α-ketol **20** (93 mg, 0.29 mmol) in methanol (4 cm^3) was added sodium borohydride (5.5 mg) at 0 °C. The mixture was stirred at the same temperature for 2 h, after which the methanol was evaporated under reduced pressure and the residue added to water. The aqueous mixture was extracted with diethyl ether and the extract was washed successively with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (3:1–2:1) to give the α-diol **21** (81.7 mg, 87%) as an oil (Found: C, 75.3; H, 10.4; N, 4.2. $C_{20}H_{33}NO_2$ requires C, 75.19; H, 10.41; N, 4.38); ν_{max}(neat)/cm^{-1} 3450, 2210, 1635 and 1450; δ_H(500 MHz) 1.16 (3 H, s, 13-Me), 1.17 (6 H, d, *J* 6.8, CH*Me*$_2$), 1.20 (3 H, s, 13-Me), 1.41 (1 H, m, 11-H), 1.58 (1 H, m, 11-H), 1.63 (3 H, s, 9-Me), 1.84 (3 H, s, 5-Me), 2.07 (1 H, m, 10-H$_a$), 2.19 (4 H, m, 6 and 7-H), 2.26 (1 H, m, 10-H$_b$), 2.33 (1 H, br s, OH), 2.47 (1 H, br s, OH), 2.53 (1 H, sept, *J* 6.8, C*H*Me$_2$), 3.33 (1 H, br d, *J* 10.3, 12-H), 5.17 (1 H, br m, 8-H), 6.27 (1 H, d, *J* 11.5, 4-H) and 6.79 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 16.0 (q), 17.3 (q), 21.6 (q) ×2, 23.2 (q), 26.1 (t), 26.4 (q), 29.7 (t), 33.2 (d), 36.6 (t), 40.0 (t), 72.9 (s), 78.1 (d), 117.6 (s), 117.7 (s), 121.7 (d), 123.8 (d), 135.8 (s), 137.7 (d) and 147.6 (s); *m*/*z* 319 (M$^+$, 0.5%), 301 (0.5%), 260 (1), 153 (40), 71 (80) and 59 (100).

(2*Z*,4*E*,8*E*)-11-Formyl-5,9-dimethyl-2-(1-methylethyl)undeca-2,4,8-trienenitrile 24

To a solution of the α-diol **21** (504 mg, 1.58 mmol) in methanol (15 cm^3) and water (3 cm^3) was added sodium metaperiodate (405 mg, 1.90 mmol), and the mixture was stirred at room temperature overnight. After this the methanol was evaporated under reduced pressure, and the residue was dissolved in diethyl ether and water. The organic layer was separated and the water layer was extracted with diethyl ether. The combined organic layers and extracts were washed successively with water, aq. $NaSO_3$ and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (10:1) to give the aldehyde **24** (364 mg, 89%) as an oil, ν_{max}(neat)/cm^{-1} 2200, 1725, 1630 and 1440; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.9, CH*Me*$_2$), 1.63 (3 H, s, 9-Me), 1.82 (3 H, s, 5-Me), 2.17 (4 H, m, 6 and 7-H), 2.33 (2 H, t, *J* 7.6, 10-H), 2.52 (2 H, m, 11-H and C*H*Me$_2$), 5.13 (1 H, m, 8 H), 6.27 (1 H, d, *J* 11.5, 3-H), 6.81 (1 H, d, *J* 11.5, 4-H) and 9.75 (1 H, t, *J* 1.9, 12-H); δ_C(125 MHz) 16.1 (q), 17.3 (q), 21.6 (q) ×2, 26.1 (t), 31.8 (t), 33.3 (d), 39.9 (t), 42.1 (t), 117.5 (s), 117.8 (s), 121.9 (d), 124.3 (d), 134.0 (s), 137.6 (d), 147.4 (s) and 202.5 (s); *m*/*z* 259 (M$^+$, 4%), 258 (5), 216 (3), 148 (15), 134 (25) and 93 (100) (Found: M$^+$, 259.1954. $C_{17}H_{25}NO$ requires *M*, 259.1935).

The aldehyde **24** was also obtained from **18** without isolation of **20** and **21** by a one-pot reaction. Thus to crude **20** formed from **18** (1.25 g, 5.37 mmol), after removal of unchanged **10**, was added $NaBH_4$ (66 mg, 1.74 mmol) in methanol (10 cm^3) with stirring on an ice–water bath. After being stirred for 30 min, the solution was treated with a mixture of $NaIO_4$ (1.71 g, 8.05 mmol), methanol (10 cm^3) and water (4 cm^3) and the whole stirred vigorously for 10 h. Work-up and chromatography of the reaction mixture in a way similar to that described above gave **24** (1.24 g, 83%).

(2*Z*,4*E*)-5,9-Dimethyl-2-(1-methylethyl)-8-vinyloxydeca-2,4,9-trienenitrile 19

A mixture of the allylic alcohol **18** (150 mg, 0.64 mmol) and mercury(II) acetate (30 mg, 0.09 mmol) in ethyl vinyl ether (8 cm^3) was heated under reflux for 10 h. After being diluted

with diethyl ether, the mixture was washed with aqueous NaOH (1 mol dm^{-3}), dried ($MgSO_4$) and concentrated. The residue was chromatographed (5:1) to give the vinyl ether **19** (89 mg, 53%) as an oil, along with unchanged **18** (8 mg, 5%), ν_{max}(neat)/cm^{-1} 2210, 1640 and 1450; δ_H(250 MHz) 1.14 (6 H, d, *J* 6.8, CHMe_2), 1.65–1.90 (2 H, m, 7-H), 1.67 (3 H, s, 9-Me), 1.82 (3 H, d, *J* 1.2, 5-Me), 2.15 (2 H, m, 6-H), 2.51 (1 H, sept, *J* 6.8, C*H*Me_2), 3.98 (1 H, dd, *J* 1.4 and 6.5, OCH=CH_2), 4.03 (1 H, *J* 6.0 and 7.2, 8 H), 4.28 (1 H, dd, *J* 1.4 and 14.2, OCH=CH_2), 4.91 (1 H, br s, CC=CH_2), 4.93 (1 H, br s, CC=CH_2), 6.25 (1 H, dd, *J* 6.5 and 14.2, OC*H*=CH_2), 6.27 (1 H, d, *J* 11.5, 4-H) and 6.79 (1 H, d, *J* 11.5, 3-H).

A solution of the vinyl ether **19** (43 mg, 0.17 mmol) in toluene (2 cm^3) was heated under reflux for 7 h and then concentrated. The residue was chromatographed (5:1) to give the aldehyde **24** (41 mg, 95%) contaminated with 11% of its 8*Z*-isomer, as indicated by GLC.

(2*Z*,4*E*,8*E*,12*E*)-13-Ethoxycarbonyl-5,9-dimethyl-2-(1-methylethyl)tetradeca-2,4,8,12-tetraenenitrile 26

To a solution of the aldehyde **24** (130 mg, 0.5 mmol) in methylene dichloride (4 cm^3) under an argon atmosphere was added the phosphorane **25** (217 mg, 0.6 mmol), and the mixture was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure from the mixture, diethyl ether–hexane (1:1) was added to the residue. The resultant mixture was filtered and the filtrate was concentrated to give a crude product of ester as a 97.1:2.9 mixture of **26** and its geometrical isomer according to GLC analysis. Compound **26** (155 mg, 90%) was obtained by flash column chromatography (8:1) as an oil, ν_{max}(neat)/cm^{-1} 2210, 1710, 1640 and 1445; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.8, CHMe_2), 1.28 (3 H, t, *J* 6.9, CH_2CH_3), 1.63 (3 H, s, 9-Me), 1.83 (6 H, s, 5 and 13-Me), 2.10 (2 H, t, *J* 7.6, 10-H), 2.17 (4 H, m, 6 and 7-H), 2.26 (2 H, br q, *J* 7.9, 11-H), 2.53 (1 H, sept, *J* 6.8, C*H*Me_2), 4.18 (2 H, q, *J* 7.6, 12-H), 5.13 (1 H, br m, 8-H), 6.29 (1 H, d, *J* 11.5, 4-H), 6.73 (1 H, dd, *J* 6.6, 8.3, 12-H) and 6.82 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 12.4 (q), 14.3 (q), 16.0 (q), 17.4 (q), 21.6 (q) × 2, 26.3 (t), 27.3 (t), 33.3 (d), 38.2 (t), 40.1 (t), 60.3 (t), 117.5 (s), 117.8 (s), 121.8 (d), 124.0 (d), 127.8 (s), 134.9 (s), 137.6 (d), 141.8 (d), 147.6 (s) and 168.2 (s); *m*/*z* 343 M^+, 8%), 297 (15), 216 (10), 195 (25), 149 (30), 121 (100) and 93 (80) (Found: M^+, 343.2567. $C_{22}H_{33}NO_2$ requires *M*, 343.2510).

(2*Z*,4*E*,8*E*,12*E*)-14-Hydroxy-5,9,13-trimethyl-2-(1-methylethyl)tetradeca-2,4,8,12-tetraenal 31

To a solution of the cyano ester **26** (175 mg, 0.51 mmol) in toluene (5 cm^3) under argon atmosphere was added a 1 mol dm^{-3} solution of DIBAL in toluene (1.8 cm^3) at −78 °C. The mixture was stirred at the same temperature for 1 h, after which 1 mol dm^{-3} aqueous oxalic acid (4.2 cm^3) was added to it. The cooling bath was removed, and the mixture was vigorously stirred for 2 h. The organic layer was separated, washed with water, saturated aqueous $NaHCO_3$ and brine, dried, filtered and concentrated. The residue was chromatographed (7:1) to give the hydroxy aldehyde **31** (123 mg, 79%) as an oil, ν_{max}(neat)/cm^{-1} 3430, 1670, 1630 and 1450; δ_H(250 MHz) 1.17 (6 H, d, *J* 6.7, CHMe_2), 1.62 (3 H, s, 9-Me), 1.67 (3 H, s, 13-Me), 1.84 (3 H, d, *J* 1.2, 5-Me), 2.0–2.2 (8 H, m, 6, 7, 10 and 11-H), 2.53 (1 H, sept, *J* 6.7, C*H*Me_2), 3.99 (2 H, s, 12-H), 5.11 (1 H, br m, 8-H), 5.39 (1 H, br t, *J* 5.5, 12-H), 6.80 (1 H, d, *J* 12, 4-H), 7.11 (1 H, d, *J* 12, 3-H) and 10.25 (1 H, s, CHO); δ_C(62.5 MHz) 13.6 (q), 16.0 (q), 16.7 (q), 22.0 (q) × 2, 26.1 (t), 26.2 (t), 27.0 (d), 39.2 (t), 40.7 (t), 68.9 (t), 117.8 (d), 123.5 (d), 125.8 (d), 134.8 (s), 135.6 (s), 138.1 (d), 142.1 (s), 148.4 (s) and 190.6 (d).

(2*Z*,4*E*,8*E*,12*E*)-14-Chloro-5,9,12-trimethyl-2-(1-methylethyl)-tetradeca-2,4,8,12-tetraenal 2, from 31

To a stirred solution of lithium chloride (64 mg, 1.5 mmol), 2,6-dimethylpyridine (0.23 cm^3, 2.0 mmol) and the hydroxy aldehyde **31** (305, 1.0 mmol) in DMF (1.0 cm^3) at 0 °C was added MsCl (160 mg, 1.4 mmol). After the mixture had been stirred for 8 h at the same temperature, water and diethyl ether were added to it. The organic layer was separated, washed successively with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (20:1), to afford the chloride **2** (281 mg, 87%) as an oil, the spectra of which were identical with those of previously prepared material.[2]

(2*Z*,4*E*,8*E*)-13-Hydroxy-5,9,13-trimethyl-2-(1-methylethyl)-12-methylsulfonyloxytetradeca-2,4,8-trienenitrile 22

To a solution of the α-diol **21** (312 mg, 0.98 mmol) in pyridine (1 cm^3) at 0 °C was added MsCl (123 mg, 1.08 mmol), and the mixture was stirred overnight at room temperature. Ice–water was then added to the mixture after which it was extracted with diethyl ether (×3). The combined extracts were washed successively with water, 2 mol dm^{-3} hydrochloric acid, water and saturated aqueous $NaHCO_3$, and then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (5:1) to give the α-diol monomesylate **22** (365 mg, 94%) as an oil, ν_{max}(neat)/cm^{-1} 3530, 2210, 1635, 1470 and 1450; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.8, CHMe_2), 1.24 (3 H, s, 13-Me), 1.26 (3 H, s, 13-Me), 1.62 (3 H, s, 9-Me), 1.71 (2 H, m, 11-H), 1.84 (3 H, s, 5-Me), 2.09 (1 H, m, 10-H_a), 2.21 (4 H, m, 6 and 7-H), 2.23 (1 H, m, 10-H_b), 2.53 (1 H, sept, *J* 6.8, C*H*Me_2), 3.13 (3 H, s, SO_2Me), 4.55 (1 H, dd, *J* 4.0 and 8.5, 12-H), 5.18 (1 H, br m, 8-H), 6.27 (1 H, d, *J* 11.5, 4-H) and 6.80 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 16.0 (q), 17.3 (q), 21.6 (q) × 2, 23.5 (q), 26.1 (t), 26.9 (q), 29.2 (t), 33.2 (d), 35.9 (t), 38.8 (q), 39.9 (t), 72.3 (s), 90.1 (d), 117.5 (s), 117.6 (s), 121.7 (d), 124.4 (d), 134.3 (s), 137.7 (d) and 147.6 (s); positive SIMS (matrix: 3-nitrobenzyl alcohol) *m*/*z* 398 (M^+ + 1, 22%), 301 (98) and 284 (100) (Found: M^+ + 1, 398.2425. $C_{21}H_{36}NO_4S$ requires *M* + 1, 398.2363).

(2*Z*,4*E*,8*E*)-12,13-Epoxy-5,9,13-trimethyl-2-(1-methylethyl)-tetradeca-2,4,8-trienenitrile 27

To a solution of the monomesylate **22** (246 mg, 0.62 mmol) in methanol (3 cm^3) was added anhydrous potassium carbonate (257 mg, 1.9 mmol) at 0 °C, and the mixture was stirred for 2 h at the same temperature. The mixture was evaporated under reduced pressure, and water was added to the residue. The mixture was extracted with diethyl ether, and the extract was washed successively with water and brine, and then dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (7:1) to give the epoxide **27** (172 mg, 92%) as an oil, ν_{max}(neat)/cm^{-1} 2220, 1640 and 1455; δ_H(500 MHz) 1.17 (6 H, d, *J* 6.8, CHMe_2), 1.26 (3 H, s, 13-Me), 1.30 (3 H, s, 13-Me), 1.6–1.7 (2 H, m, 11-H), 1.64 (3 H, s, 9-Me), 1.83 (3 H, s, 5-Me), 2.1–2.2 (2 H, m, 10-H), 2.18 (4 H, m, 6 and 7-H), 2.53 (1 H, sept, *J* 6.8 C*H*Me_2), 2.70 (1 H, t, *J* 6.3, 12-H), 5.15 (1 H, br m, 8-H), 6.28 (1 H, d, *J* 11.5, 4-H) and 6.82 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 16.0 (q), 17.3 (q), 18.7 (q), 21.6 (q) × 2, 24.9 (q), 26.2 (t), 27.4 (q), 33.3 (d), 36.3 (t), 40.1 (t), 58.3 (s), 64.1 (d), 117.5 (s), 117.7 (s), 121.8 (d), 123.8 (d), 135.0 (s), 137.6 (d) and 147.6 (s); positive SIMS (matrix: 3-nitrobenzyl alcohol) *m*/*z* 302 (M^+ + 1, 100%), 216 (5) and 153 (20) (Found: M^+ + 1, 302.2492. $C_{20}H_{32}NO$ requires *M* + 1, 302.2501).

(2*Z*,4*E*,8*E*)-12-Hydroxy-5,9,13-trimethyl-2-(1-methylethyl)-tetradeca-2,4,8,13-tetraenenitrile 28

The procedure described for compound **18** was employed with the epoxide **27** (186 mg, 0.62 mmol). Flash column chromatography (6:1) of the residue afforded the allylic alcohol **28** (160 mg, 86%) as an oil (Found: C, 79.7; H, 10.6; N, 4.5. $C_{20}H_{31}NO$ requires C, 79.68; H, 10.37; N, 4.65); ν_{max}(neat)/cm^{-1} 3380, 2220, 1635 and 1450; δ_H(500 MHz) 1.16 (6 H, d, *J*

6.8, $CHMe_2$), 1.6–1.7 (2 H, m, 11-H), 1.62 (3 H, s, 9-Me), 1.73 (3 H, s, 13-Me), 1.83 (3 H, s, 5-Me), 2.03 (2 H, m, 10-H), 2.18 (4 H, m, 6 and 7-H), 2.52 (1 H, sept, *J* 6.8, $CHMe_2$), 4.04 (1 H, br t, *J* 7.2, 12-H), 4.83 and 4.93 (each 1 H, s, $C{=}CH_2$), 5.14 (1 H, br m, 8-H), 6.27 (1 H, d, *J* 11.5, 4-H) and 6.82 (1 H, d, *J* 11.5, 3-H); δ_C(125 MHz) 16.0 (q), 17.3 (q), 17.6 (q), 21.6 (q) ×2, 26.2 (t), 33.1 (t), 33.3 (d), 35.6 (t), 40.1 (t), 75.5 (d), 111.0 (t), 117.6 (s), 117.7 (s), 121.9 (d), 123.6 (d), 135.6 (s), 137.7 (d), 147.5 (s) and 147.6 (s); *m/z* 301 (M^+, 4%), 284 (12), 135 (60) and 93 (100).

(2*Z*,4*E*,8*E*,12*E*)-14-Chloro-5,9,13-trimethyl-2-(1-methylethyl)-tetradeca-2,4,8,12-tetraenenitrile 32

To a stirred solution of the allylic alcohol **28** (12.6 g, 41.9 mmol) in hexane (127 cm^3) under an argon atmosphere at 0 °C was added thionyl chloride (3.21 cm^3). The mixture was kept at room temperature for 15 h, after which saturated aq. $NaHCO_3$ was added to it at 0 °C with stirring. The organic layer was separated, and the water layer was extracted with portions of diethyl ether. The combined organic layers and extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (20:1) to afford a mixture (12.0 g, 90%) of the desired chloride **32** together with compound **30** as an oil; the ratio of products **32**:**30** was determined as 80:20 by capillary GLC.

Conversion of 32 contaminated with 30 into 1

To a stirred solution of compound **32** contaminated with **30** (2.48 g, 7.76 mmol) in toluene (43 cm^3) at −20 °C was added dropwise DIBAL (1 mol dm^{-3} solution in toluene; 8.5 cm^3). After the mixture had been stirred at the same temperature for 10 min, 10% aq. oxalic acid (31 cm^3) was added to it, and stirring continued for an additional 2 h at room temperature. The organic layer was separated and the aqueous layer was extracted with toluene. The combined organic layers were washed with water, dried (Na_2SO_4) and filtered. The filtrate (almost 80 cm^3) was immediately used in the next step.

Trimethylsilyl cyanide (1.34 cm^3, 10.1 mmol) and Bu_4NCN (110 mg, 0.4 mmol) were added to the filtrate and the mixture was stirred at room temperature for 2 h; after this it was concentrated to give, as an oily residue (5.69 g), the crude cyanohydrin trimethylsilyl ether of **2**.

Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} THF solution; 27.2 cm^3) was diluted with THF (130 cm^3) and warmed to 55 °C. To the stirred solution, at the same temperature, under an argon atmosphere, was added dropwise the above residue in THF (130 cm^3). After the addition was completed, the mixture was cooled to 4 °C, treated with water (0.5 cm^3) and concentrated. The residue was diluted with ethyl acetate (130 cm^3) and washed with water. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated to afford an oily brown residue (3.32 g). A stirred mixture of the residue and water (3.5 cm^3) in THF (39 cm^3) was cooled to 4 °C, and Bu_4NF (1 mol dm^{-3} THF solution; 0.54 cm^3) was added to it. After being kept for 12 h at the same temperature, the mixture was concentrated and the residue diluted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated to give an oily dark brown residue (2.46 g).

To a chiral reducing reagent prepared from (1*R*,2*S*)-(−)-*N*-methylephedrine (2.39 g), $LiAlH_4$ (488 mg, 12.9 mmol) and *N*-ethylaniline (3.21 g, 26.5 mmol) according to a previously reported procedure[2] was added dropwise over 20 min to the residue in diethyl ether (24 cm^3) at −20 °C. The mixture was stirred for 15 min at the same temperature and then treated with 1 mol dm^{-3} aqueous HCl (100 cm^3). The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were washed successively with 1 mol dm^{-3} aqueous HCl and water, dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed (20:3) to give optically active **1** (89.1% ee, HPLC analysis, column: Daicel Chiralcell OD®) (895 mg, 40%), from which **1** of >99% ee (490 mg, 55%), mp 56–57 °C, was obtained by recrystallization from aqueous ethanol.

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