# Synthesis of the Chiral Upper Fragment of Tetronolide

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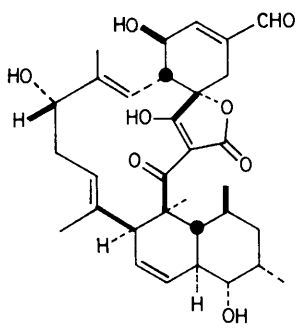
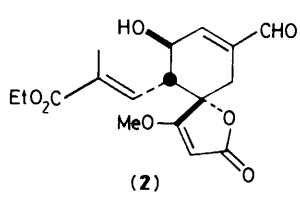
The chiral upper fragment (**3**) of tetronolide (**1**) was synthesized *via* spiroannulation of optically active cyclohexanone derivative (**5**) with *trans*-β-methoxyacrylate and subsequent functionalization of the resulting spirotetronate (**6**).

Previously we reported the synthesis of the racemic upper fragment (**2**) of tetronolide (**1**).[1] Now we describe a chiral synthesis of an advanced spirotetronic acid structure (**3**), which has different protecting groups suitable for the total synthesis of (**1**),[2] by utilizing our improved technique in Schmidt spiroannulation.[3]

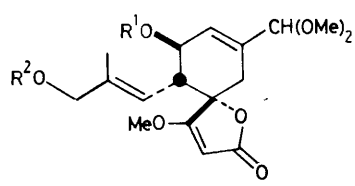
The starting material, (1*R*,2*S*)-(**4**) [98% enantiomeric excess (e.e.)],[4] was first converted to α-silyloxymethyl ketone (**5**) by three steps (Scheme 1): reduction of the ester group, selective *O*-silylation of the resulting diol, and oxidation with pyridinium chlorochromate (PCC)[5] (80% overall yield). This ketone (**5**) was subjected to reaction with the β-dichlorocerium derivative of methyl *trans*-β-methoxyacrylate under controlled conditions;† the annulation product was desilylated with $Bu^n_4NF$ to give spirotetronate (**6**) in 89% yield from (**5**). Subsequent side chain extension by oxidation with PCC followed by a Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$ pro-




(**1**)



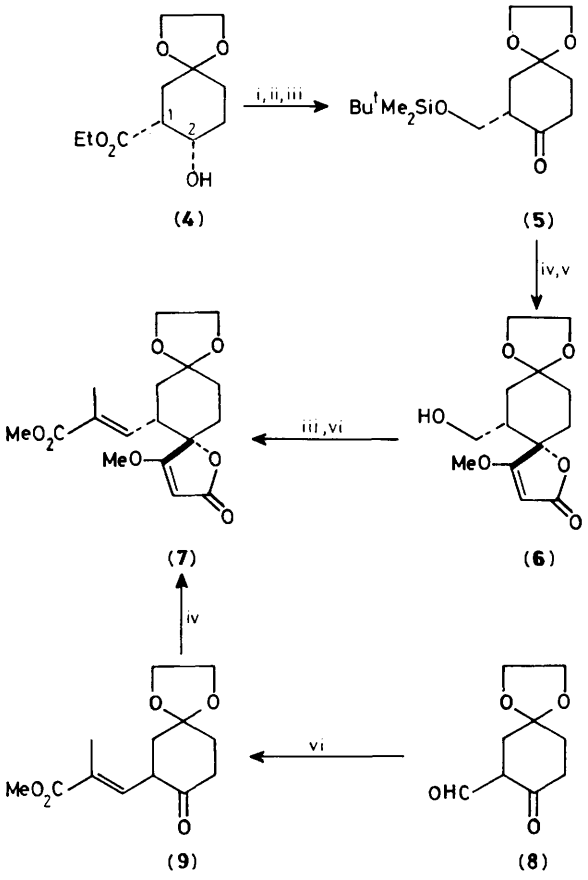

(**2**)



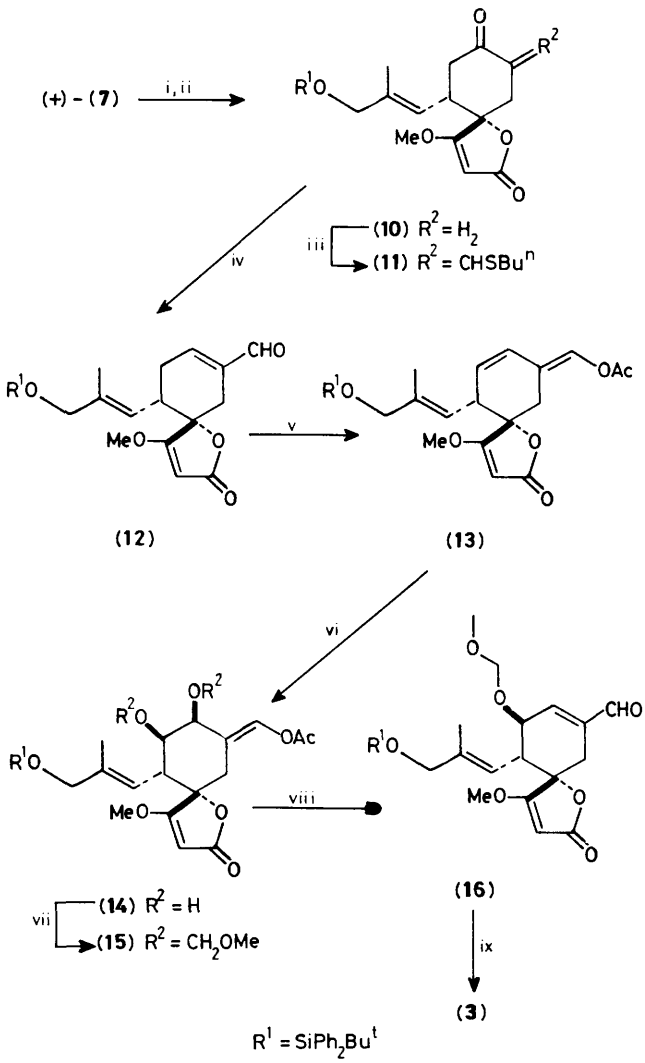

(**3**) $R^1$ = $CH_2OMe$
$R^2$ = $SiPh_2Bu^t$

† This crucial annulation was carried out as follows. A solution of lithium di-isopropylamide (LDA) [9.9 mmol in 15 ml of tetrahydrofuran (THF)–n-hexane] cooled at −90 °C was cannulated into a stirred solution of *trans*-β-methoxyacrylate (10.2 mmol in 20 ml of THF) at −90 °C. After 3 min, the resulting lithio acrylate was treated *via* a cannula with a suspension of anhydrous $CeCl_3$ (16 mmol in 10 ml of THF) cooled at −90 °C. After 5 min, a solution of (**5**) (3.2 mmol in 10 ml of THF) was added to the red suspension, and the mixture was allowed to warm to −40 °C over 1.5 h, before quenching with aqueous ammonium chloride.

This procedure is particularly useful for highly enolizable ketone and also in obtaining much higher yield than the original protocol.[3]



**Scheme 1.** *Reagents and conditions*: i, $LiBEt_3H$ (3.3. equiv.), tetrahydrofuran (THF), 0 °C, 30 min, then $H_2O_2$–NaOH–$H_2O$, room temp., 15 min; ii, $Bu^tMe_2SiCl$, imidazole, $CH_2Cl_2$, room temp., overnight; iii, PCC, $MeCO_2Na$, 3 Å molecular sieves, Celite, $CH_2Cl_2$; iv, see footnote †; v, $Bu^n_4NF$ (1 equiv.), THF, room temp.; vi, $Ph_3P{=}C(Me)CO_2Et$, benzene.



**Scheme 2.** *Reagents and conditions*: i, $LiBEt_3H$ (2 equiv.), tetrahydrofuran (THF), −80 °C, 30 min; ii, acetone–HCl (pH *ca.* 1), reflux, 4 h, then $Bu^tPh_2SiCl$, imidazole, dimethylformamide, room temp., 15 min; iii, $HCO_2Et$, MeONa, benzene, then $Bu^nSH$, camphorsulphonic acid, benzene, $MgSO_4$, room temp.; iv, $LiBEt_3H$ (1 equiv.), THF, −80 °C, 15 min, then $HgCl_2$, acetone–HCl (pH *ca.* 2), room temp., 30 min; v, $Me_3SiCl$ (4.4 equiv.), NaI (4.2 equiv.), acetic anhydride (80 equiv.), 0 to 60 °C, 40 min; vi, $OsO_4$, $Me_3N(O)$, acetone–$H_2O$, room temp.; vii, $MeOCH_2Cl$, $Pr^i_2NEt$, dimethylformamide, room temp., 12 h; viii, 5% $K_2CO_3$–MeOH (1:250), room temp., 10 min; ix, pyridinium *p*-toluenesulphonate, MeOH, room temp.

vided (**7**) (91% e.e.)‡ in 80% yield. We also prepared a racemate of (**7**) from keto ester (**9**) (90—98% yield), which was derived from keto aldehyde (**8**) by a Wittig reaction (66% yield), by application of the spiroannulation technique described above.

To introduce the conjugated aldehyde system at the six membered ring, spirotetronate (**7**) was first transformed into a keto alcohol derivative (**10**) by three steps (Scheme 2): selective reduction of the ester group with $LiBEt_3H$, deketalization, and *O*-silylation with $Bu^tPh_2SiCl$. An optically pure sample of (**10**),‡ m.p. 167—170 °C, $[\alpha]_D^{23}$ +63.3° (*c* = 1.71, $CHCl_3$), was obtained by recrystallization from di-isopropyl ether [30% yield from (**7**) without purification of the intermediates]. Then a (butylthio)methylene group was introduced at the α-position remote from the side chain to give (**11**) in *ca.* 50% yield. The ketone carbonyl of (**11**) was selectively reduced with $LiBEt_3H$, and the resulting carbinol was subjected to mercuric ion assisted hydrolysis of the thioether[6] affording the conjugated aldehyde (**12**) in 70% yield, m.p. 119—122 °C, $[\alpha]_D^{23}$ +68.9° (*c* = 1.75, $CHCl_3$).

The remaining task, introduction of β-oriented hydroxyl group at C-9, was commenced by the formation of dienol acetate (**13**) by reaction with acetic anhydride in the presence of $Me_3SiCl$ and NaI (92% yield).[7] Regio- and diastereoselective dihydroxylation of the *endo* double bond of (**13**) was achieved by a catalytic osmylation[8] to give (**14**) in 67% yield, m.p. 158—160 °C, $[\alpha]_D^{23}$ +29.98° (*c* = 1.72, $CHCl_3$). Finally, diol (**14**) was converted to bis-methoxymethyl ether (**15**) (64% yield), and it was briefly treated with methanolic potassium carbonate to afford γ-methoxymethoxy-α,β-unsaturated

‡ The optical purity was determined by $^1H$ n.m.r. (270 MHz) spectral analysis using the chiral shift reagent Eu(hfc)$_3$ = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

aldehyde (**16**) (>99% e.e.)§¶ in 86% yield, $[\alpha]_D^{23}$ +108.6° ($c$ = 0.899, $CHCl_3$). Treatment of (**16**) in methanol with pyridinium toluene-*p*-sulphonate (PPTS) provided the target compound (**3**) (>99% e.e.)‡ in high yield, $[\alpha]_D^{23}$ +110.0° ($c$ = 1.74, $CHCl_3$).

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§ This compound (+)-(**16**) failed to crystallize, whereas the racemate (±)-(**16**) prepared from (±)-(**7**) according to the same procedure (Schemes 1 and 2) was obtained as crystals, m.p. 61—64 °C.

¶ *Spectral data* for (**16**): i.r. (KBr) 1760 (C=O), 1690 (C=O), 1640 (C=C) $cm^{-1}$; $^1H$ n.m.r. (270 MHz, $CDCl_3$) 1.04 (s, 9H, $Bu^t$), 1.66 (d, $J$ 1.3 Hz, 3H, 2′-Me), 2.46 (d, $J$ 18.3 Hz, 1H, H-6), 2.75 (dt, $J$ 18.3, 2.7 Hz, 1H, H-6), 3.01 (t, $J$ 10.1 Hz, 1H, H-10), 3.36 (s, 3H, OMe), 3.78 (s, 3H, 4-OMe), 4.01 (br s, 2H, H-3′), 4.54 (dd, $J$ 10.1, 2.7 Hz, 1H, H-9), 4.66 (ABq, $J$ 6.8 Hz, 2H, $OCH_2O$), 5.03 (s, 1H, H-3), 5.33 (dd, $J$ 10.4, 1.3 Hz, 1H, H-1′), 6.84 (br s, 1H, H-8), 7.35—7.65 (m, 10H, ArH), 9.55 (s, 1H, CHO); mass spectrum (electron impact) $m/z$ 576 ($M^+$), 519 ($M^+$ − $Bu^t$, base peak).

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