Synthesis of an Isomer of the Oxaspirobicyclic Tetronic Acid Unit of the CCK-B Receptor Antagonist Tetronothiodin

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Abstract: An isomer of the oxaspirobicyclic tetronic acid unit of the CCK-B Receptor antagonist tetronothiodin, diastereoisomeric at the spiro centre, has been synthesized in five steps from dienol **4**.

Key words: tetronothiodin, Diels–Alder, Dieckmann, spiro tetronic acid, CCK

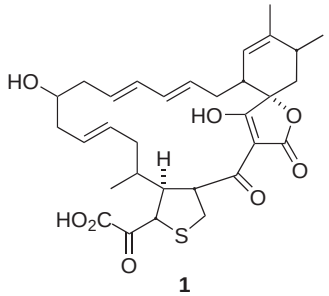
Cholecystokinin (CCK) is a 33 amino acid peptide that functions as a gastrointestinal hormone having a variety of effects including pancreatic exocrine secretion, stimulation of gut motility, and gallbladder contraction.[1] There are two types of CCK receptor: CCK-A receptors,[2] found in the periphery and in discrete regions of the central nervous system, and responsible for the satiety actions of peripherally administered CCK; and CCK-B receptors, widely distributed in the brain, which have been shown to cause appetite,[3] pain,[4] and anxiety.[5]

Tetronothiodin (**1**) is a novel brain-type CCK receptor antagonist isolated from *Streptomyces sp.* NR0489.[6] The structure is claimed on the basis of detailed spectroscopic analysis and is not supported by crystallography. The relative stereochemistry therefore remains unconfirmed at any of the asymmetric centers, and indeed none is yet proposed for two of the eight.

Our synthetic approach is designed around a flexible and convergent route, with the target molecule split into three zones: The oxaspirobicyclic unit, the unsaturated macrocycle framework, and the tetrahydrothiophene (Scheme 1).

We report herein the stereoselective synthesis in five steps of oxaspirobicycle **2**, a diastereoisomer of the proposed structure of the oxaspirobicyclic unit of **1**, suitably functionalized with hydroxyethyl and ester substituents for further elaboration (Figure 1).

The synthesis of **2** began with the preparation of the Wittig salt **3** from 3-bromopropanol and triphenyl phosphine in dry toluene under reflux, which afforded the phosphonium salt in 96% yield. Treatment of 3-hydroxypropyl phosphonium salt **3** with *n*-butyllithium at 0 °C followed by *trans*-2-methyl butenal gave (*E*,*E*)-5-methylhepta-3,5-dien-1-ol (**4**) in 84% yield (Scheme 2).[7]



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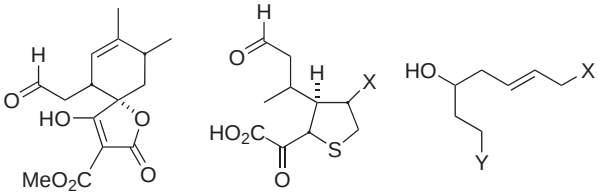
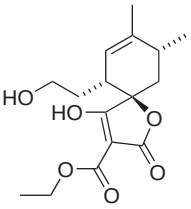
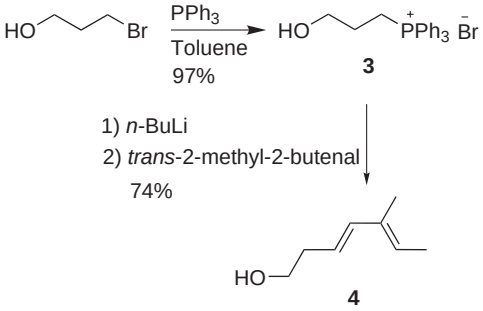


Scheme 1



2

Figure 1



Scheme 2

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Art Id.1437-2096,E;2003,0,07,1022,1024,ftx,en;D0303ST.pdf.

The preparation of diene **4** allowed the study of Diels–Alder reactions with suitable dienophiles, chosen to provide appropriate functionality in the adduct for elaboration into the spirotetronic acid moiety. Successful cycloadditions were observed with nitroethylene at room temperature in toluene (64%), phenyl vinyl sulfone at 170 °C in toluene (36%), and 2-chloroacrylonitrile at 110 °C in toluene (40%), giving **5**, **6**, and **7** respectively (Figure 2).

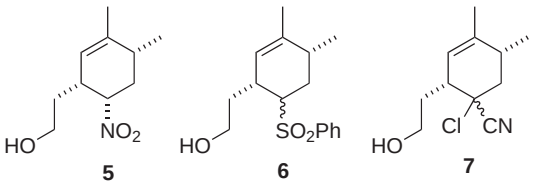
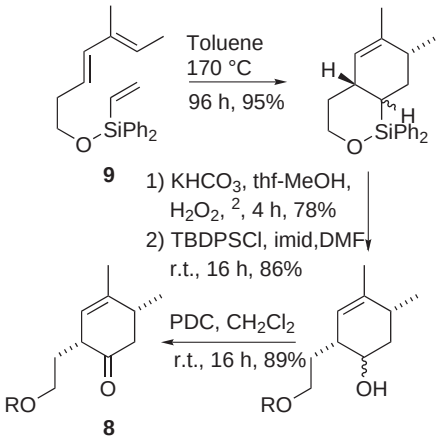


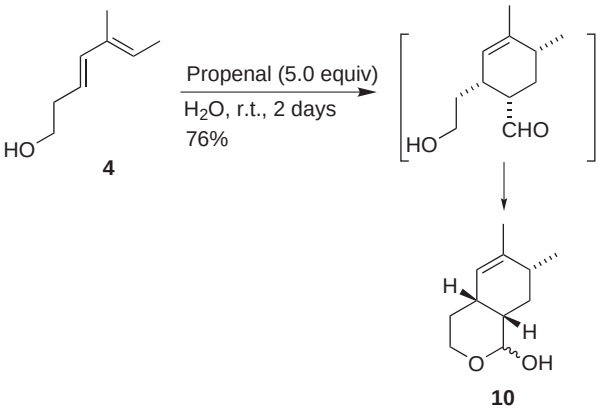
Figure 2

Construction of the spirotetronic acid requires introduction of acyl and oxygen substituents into the new six-membered ring at the *pro*-spiro centre. Unfortunately we were unable to achieve a Nef reaction with adduct **5** to generate a carbonyl group at the *pro*-spiro position, as in compound **8** (R = H), ready for functionalization as a cyanohydrin or through Wittig or similar homologation. Compound **8** (R = TBDPS) was, however, eventually prepared using an intramolecular Diels–Alder reaction of triene **9** (95%),[8] followed by Tamao-type oxidation (78%), protection of the primary alcohol, for example as a TBDPS ether (86%), and oxidation to the ketone with pyridinium dichromate (89%) (Scheme 3).



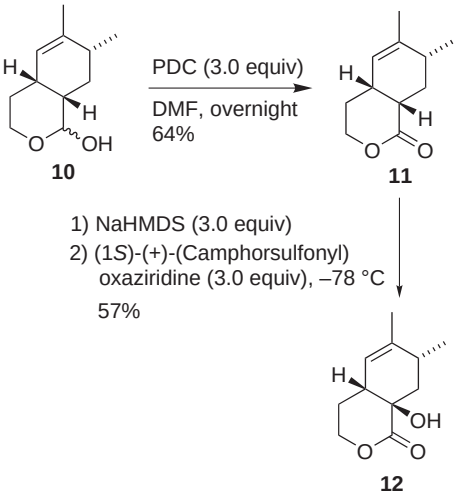
Scheme 3

Cyanohydrin formation from **8** proved poorly stereoselective, and other methods of functionalization were low-yielding. In addition, this route was rather lengthy, and we sought a more efficient approach. Attempted cycloaddition of diene **4** with ethyl acrylate had proved unsuccessful, and we were therefore delighted to discover that Diels–Alder reaction of **4** with acrolein, performed in water at room temperature, afforded the lactol *endo*-cycloadduct **10** in 76% yield,[9] in a diastereoisomeric ratio of 2:1 at the hydroxy group (Scheme 4). The Diels–Alder reaction is presumably facilitated by interaction between the hydroxy group of **4** and the aldehyde carbonyl group.



Scheme 4

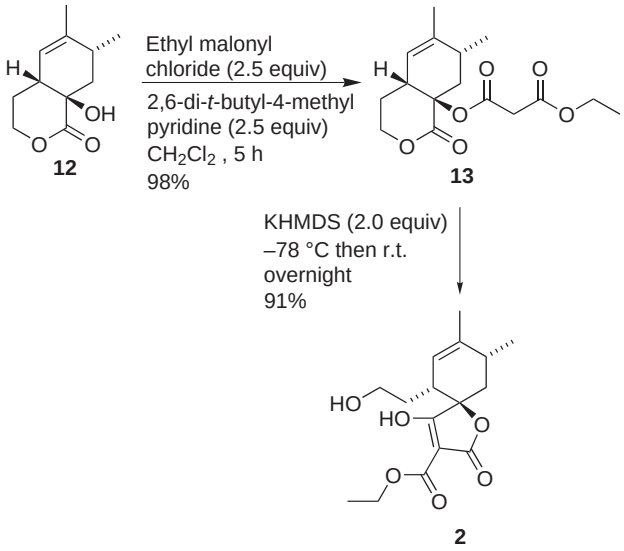
Lactol **10** was oxidized to the corresponding lactone **11** with pyridinium dichromate in *N*,*N*-dimethylformamide (Scheme 5). Introduction of the oxygen atom of the spirotetronic acid unit was accomplished by oxygenation of the enolate derived from lactone **11**. Deprotonation of **11** with sodium bis(trimethylsilyl)amide at –78 °C for 1 hour to generate the corresponding enolate, followed by treatment with (1*S*)-(+)-(10-camphorsulfonyl) oxaziridine,[10,11] afforded the hydroxylactone **12** as a single diastereoisomer in 57% yield (Scheme 5).



Scheme 5

The stereochemistry of **12** was unambiguously verified by single crystal X-ray analysis, and shown to be isomeric at this centre with the proposed structure of the natural product. Use of lithium bis(trimethylsilyl)amide gave **12** in only 31% yield, in accordance with the reported observations of Davis.[10] Hydroxylactone **12** was also derived from **11** by hydroxylation of the enolate with 2-(phenylsulfonyl)-3-phenyloxaziridine in 46% yield. Hydroxylation of the enolate derived from a chiral lactone by treatment with oxygen, to yield a 1:1 mixture of stereoisomers, has been reported;[12] similar treatment of **11**, however, provided **12** as a single isomer in 20% yield.

Formation of the spirotetronic acid requires acylation of the newly-introduced hydroxy group. We envisaged that acylation of this hydroxy group as a malonyl ester and subsequent deprotonation of the malonyl moiety might lead to intramolecular Dieckmann cyclization[13] by nucleophilic attack at the lactone carbonyl group, so generating the spirotetronic acid unit of **1**/**2**, complete with a pendant ester group for attachment to the macrocycle (Scheme 6). Hydroxylactone **12** was thus treated with excess (2.5 equiv) ethyl malonyl chloride in the presence of 2,6-di-*t*-butyl-6-methylpyridine (2.5 equiv), in dichloromethane as solvent. The acylated product **13** was obtained after a five-hour reaction time in excellent yield (98%).



Scheme 6

Treatment of malonate derivative **13** with lithium bis(trimethylsilyl)amide (2.0 equiv) overnight at room temperature did not induce product formation. Ishihara has reported that potassium bis(trimethylsilyl)amide is a much more effective reagent for Dieckmann cyclization than are the corresponding lithium or sodium derivatives.[14] We were gratified to find that the desired Dieckmann cyclization to give **2** proceeded smoothly in 91% yield upon exposure of **13** to potassium bis(trimethylsilyl)amide at –78 °C, allowing the mixture to reach room temperature, and stirring overnight.[15] The driving force is presumably the formation of the highly conjugated five-membered ring in place of the six-membered ring lactone.

Acknowledgment

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(7) The stereochemical assignment for diene **4** was based on the coupling constant between H-3 and H-4 (J = 18 Hz), consistent with the *E* isomer.

(8) Triene **9** was prepared in 82% yield by reaction of alcohol **4** with diphenylvinylsilyl chloride in dichloromethane at r.t. in the presence of triethylamine.

(9) The stereochemical assignment for lactol **10** was based on NOE data and on the coupling constant between the hydrogen atoms at the ring junction positions (J = 4.5 Hz), consistent with the *cis* isomer.

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(15) Analytical data: IR(neat): ν_{max} = 3378, 2923, 1782, 1613 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.74–0.84 (1 H, m), 1.1 (3 H, d, J = 5.2 Hz), 1.19 (1 H, s), 1.31 (3 H, t, J = 8.0 Hz), 1.41–1.49 (1 H, m), 1.60 (3 H, s), 1.76–1.79 (2 H, m), 1.97–2.03 (1 H, m), 2.33–2.40 (2 H, m), 3.59–3.71 (2 H, m), 4.3 (2 H, q, J = 8.0 Hz), 5.3 (1 H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 194, 167, 166, 138, 121, 95, 85, 62, 60, 41, 36, 35, 31, 23, 19, 15. MS (EI): *m/z* (%) = 310 (100) [M^+] , 199, 134, 120, 91, 60. Found: 310.14124; $C_{16}H_{22}O_6$ requires 310.14164.