OXIDATION CHEMISTRY OF A cis-2-(3-FURYLIDENE)ETHANOL

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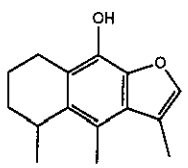
Abstract - Submission of the tri-*n*-butylstannylmethyl ether (**9**) of furylcarbinol (**8**) to Still rearrangement leads stereoselectively to **10** as the exclusive product. The cis-oriented nature of the hydroxyethyl and 3-furyl functional groups in **10** is cause for ready ring closure either to benzofuran (**10**) or lactone (**13**) depending upon conditions.

The number of furanosesquiterpenes that has been discovered in recent years has grown substantially in number and in structural variety. Modified eremophalanes such as cacalol (**1**)[2-4] and maturinone (**2**)[5] represent the linear tricyclic extreme, while tobagolide (**3**)[6,7] exemplifies the more complex pseudopterane class produced by gorgonian corals. While considering a potential route to spiniferin I (**4**),[8,9] we were struck by the paucity of routes that involve the tactic



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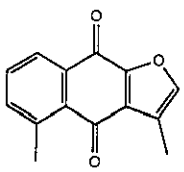

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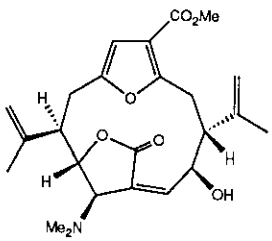

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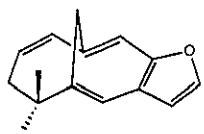

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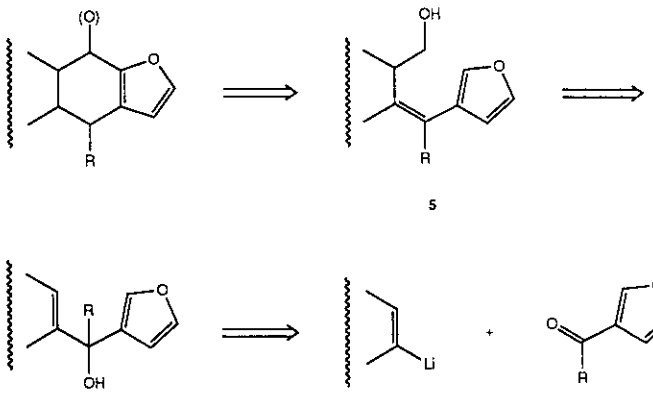
of penultimate ring B closure. For this reason, an assessment was initiated of the merits of a retrosynthetic pathway modeled upon Scheme I. As matters have turned out, the oxidation chemistry observed for an intermediate related to **5** has proven to be sufficiently exceptional as to constitute the subject of the present report.

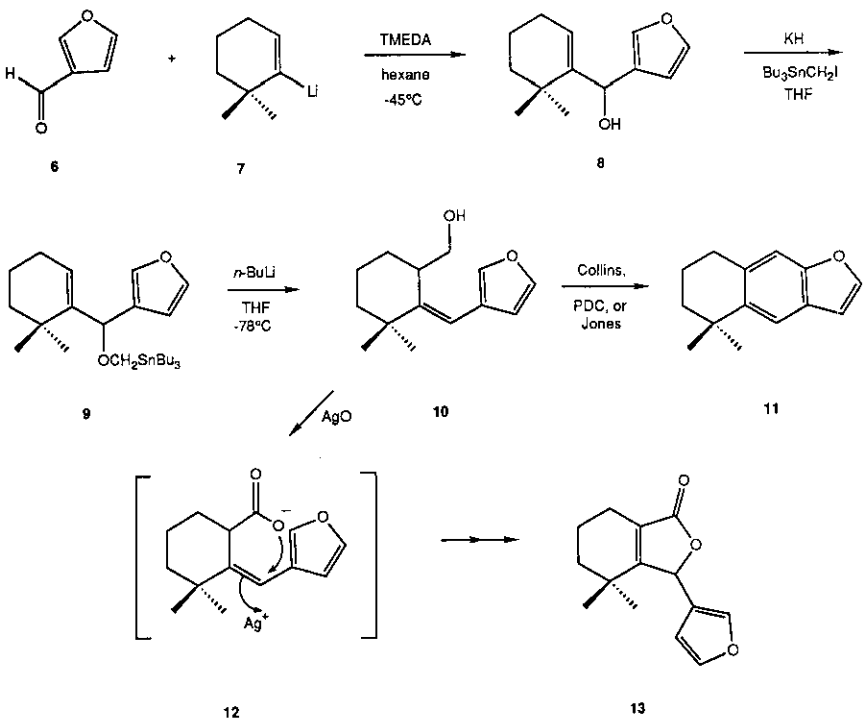
A principal advantage offered by Scheme I is the ready introduction of the furan ring via condensation of a simple carbonyl derivative with a vinyl carbanion. The focal point of the strategy is suitable introduction of the remaining carbon atom via [2,3] sigmatropic shift within an α-alkoxy anion. Such processes are well known,[10] the particular variant which utilizes tin-lithium exchange having been developed by Still.[11]

Scheme I



Of the methods investigated to prepare 3-furaldehyde (**6**), the most efficient involved oxidation of the alcohol with pyridinium chlorochromate.[12] Since **6** proved to be a light-, air-, and acid-sensitive substance, this aldehyde was stored at -10°C in the dark under nitrogen and invariably used within 24 h. 1-Lithio-6,6-dimethylcyclohexene (**7**) was obtained by Shapiro degradation[13] of the benzenesulfonylhydrazone of 2,2-dimethylcyclohexanone.[14] Condensation of **6** with **7** gave the allylic alcohol (**8**) in 58% yield after chromatography (Scheme II).

Scheme II



The derived tri-*n*-butylstannyl ether (**9**), prepared in standard fashion (96%),[11,15] is in principle capable of [2,3] sigmatropic rearrangement in either of two directions. Although the involvement of furan rings in such transformations has been reported,[16] the presence of an isolated double bond was expected to direct matters away from disruption of heterocyclic aromaticity. Indeed, exposure of **9** to *n*-butyllithium in tetrahydrofuran at -78°C gave uniquely the homoallylic alcohol (**10**).

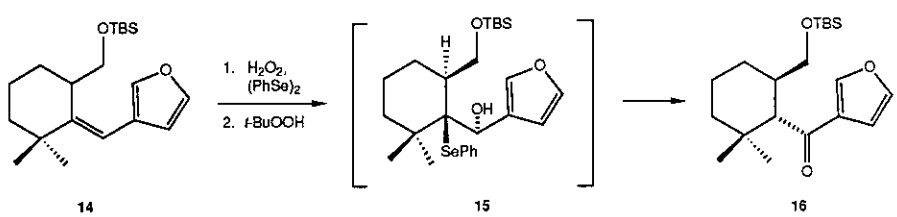
Inspection of the Newman projections pictured in Figure 1 gave rise to the prediction that a single double bond isomer would be formed. Rearrangement is presumed to involve a co-planar pπ-orbital/C-O bond alignment as shown. That

Figure 1. Transition states for the [2,3] sigmatropic rearrangement of trans-lithiated **9**.

rotamer in which steric interaction with the gem-dimethyl group is minimized has the furan ring oriented toward the cyclohexenyl double bond. Therefore, the new site of unsaturation that develops necessarily holds the furan ring cis to the hydroxymethyl substituent.

When **10** was treated with Jones reagent in anticipation of carboxylic acid formation, a dark reaction mixture was produced. Amidst the numerous compounds formed, only benzofuran (**11**) could be identified. In light of the less acidic nature of pyridinium dichromate,[17] recourse was next made to this oxidant. Once again, **11** was formed. Furthermore, it now proved to be the sole product (49% isolated). Thus, even the so-called "neutral conditions" offered by PDC was sufficient to lead to cyclization. When Collins reagent was tested, the benzofuran was obtained in 78% yield. It would appear, therefore, that the proximal furan ring is sufficiently nucleophilic to intercept the chromate intermediate intramolecularly prior to its capture by external nucleophiles.

In an attempt to increase operation of the latter chemistry, **10** was also oxidized with the alkaline agents, nickel peroxide[18] and silver(II) oxide.[19] While the nickel reagent failed to induce reaction, the effect of AgO was to promote the conversion of **10** to the unsaturated lactone (**13**). This ring closure presumably operates following transformation into the carboxylate salt, with the latter undergoing intramolecular cyclization by means of nucleophilic attack on the Ag(I)-complexed olefin as depicted in **12**.



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In light of these developments, one must guard against premature ring closure if furan annulation is to be accomplished under controlled conditions. Suitable preliminary structural modifications can be realized if the hydroxyl group is first protected, as for example in **14** → **16**,[20] but allied preparative routes to tricyclic systems of this type need to be thoughtfully devised.

EXPERIMENTAL SECTION

3-Furaldehyde (6). Pyridinium chlorochromate[21] (108 g, 0.5 mol) which had been powdered was slurried in dry dichloromethane (800 ml) along with anhydrous sodium acetate (10.3 g, 0.125 mol) by mechanical stirring under a drying tube. A dichloromethane solution (100 ml) of 3-(hydroxymethyl)furan[22] (24.5 g, 0.25 mol) was added slowly to the oxidant with simultaneous cooling in an ice bath. After being stirred at room temperature for 3 h, the mixture was diluted with ether (2500 ml) and filtered through a column of Florisil. The filtrate was carefully evaporated and the residue was distilled to give 13.0 g (54%) of **6** as a colorless oil, bp 54-58°C at 24 Torr (lit.[23] bp 48°C at 20 Torr); ^{1}H nmr (90 MHz, $CDCl_3$) δ 9.90 (s, 1 H), (d, J = 1 Hz, 1 H), 7.45 (m, 1 H), 6.78 (d, J = 2 Hz, 1 H).

1,1-Dimethyl-2-[3-(hydroxymethylfuryl)]cyclohex-2-ene (8). A three-necked flask fitted with a septum, nitrogen inlet, and Erlenmeyer flask , containing 2,2-dimethylcyclohexanone benzenesulfonylhydrazone (5.60 g, 20.0 mmol) and connected by a short piece of Gooch tubing, was charged with dry N,N,N',N'-tetramethylethylene-diamine (60 ml) and *n*-butyllithium in hexane (1.6 M, 38 ml, 60 mmol). The solution was cooled to -45°C and the solid benzenesulfonyl-hydrazone was added in portions. After complete addition (15 min), the red solution was stirred at -5°C for 15 min before being warmed to room temperature during 1 h. When nitrogen evolution ceased, the solution was recooled to -45°C and 3-furaldehyde (4.80 g, 50 mmol) was introduced via syringe. The reaction mixture lightened and was slowly warmed to room temperature over several hours. The beige solution was slowly poured into water and diluted with ether. The organic layer was consecutively extracted with water (2 x 100 ml), saturated sodium bisulfite solution (100 ml), saturated copper sulfate solution (100 ml), and brine prior to drying. The concentrated residue was quickly chromatographed on silica gel to remove low rf impurities, and the product was separated from *n*-butyl-3-furylcarbinol by high pressure liquid chromatography. There was obtained 2.40 g (58%) of **8**; ^{1}H nmr (90 MHz, $CDCl_3$) δ 7.33 (br s 2 H), 6.27 (t, J = 2 Hz, 1 H), 5.85 (t, J = 4 Hz, 1 H), 5.23 (br s, 1 H), 2.2-1.8 (m, 3 H), 1.7-1.3 (m, 4 H), 1.16 (s, 3 H), 0.96 (s, 3 H); ms *m/z* (M^+-H_2O) calcd 188.1201, obsd 188.1205.

1,1-Dimethyl-2-(O-tri-n-butylstannylmethyl)-3-(hydroxymethylfuryl)cyclohex-2-ene (9). Potassium hydride in oil (60 mg of 24%, 1.5 mmol) was washed free of oil with hexane (3 x 2 ml) and slurried in dry tetrahydrofuran (5 ml) under nitrogen. Alcohol **8** (206 mg, 1.0 mmol) was added, the mixture was stirred for 1 h, and tri-*n*-butyl-stannyliodo-methane[11a,15] (441 mg, 1.0 mmol) was added. The mixture was stirred at room temperature for 1 h before being quenched with several drops of methanol, poured into ether and water, and separated into phases. The organic layer was washed with water and brine, then dried over magnesium sulfate. The evaporated residue was chromatographed (silica gel, elution with hexane) to give in addition to a small amount of recovered **8** the ether (**9**) (392 mg, 96%); ^{1}H

nmr (90 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 6.25 (m, 1 H), 5.65 (t, J = 4 Hz, 1 H), 4.50 (s, 1 H), 3.7-3.2 (m, 2 H), 3.58 (s, 2 H), 2.2-0.7 (m, 39 H); ms *m/z* (M^+-Bu_3Sn) calcd 219.1385, obsd 219.1368.

1,1-Dimethyl-2-(3-furylidene)-3-(hydroxymethyl)cyclohexane (10). Tri-*n*-butylstannyl ether (**9**) (392 mg, 0.755 mmol) was dissolved in dry tetrahydrofuran (10 ml) and cooled to -78°C. To the cold solution was added *n*-butyllithium in hexane (1.6 *M*, 0.62 ml, 1.0 mmol) via syringe, and the brown solution was stirred in the cold for 30 min. The reaction mixture was quenched with several drops of saturated ammonium chloride solution. Ether (10 ml) was added and the organic phase was separated, extracted with brine, dried over magnesium sulfate, and evaporated. The resulting residue was chromatographed (silica gel, elution with 50% ether/hexane) to give the oily alcohol (**10**) (128 mg, 77%); ir (neat, cm^{-1}) 3350, 2920, 1460, 1105, 1040, 866; ^1H nmr (90 MHz, $CDCl_3$) δ 7.50 (m, 1 H), 2.65 (br s, 1 H), 2.4-1.4 (m, 6 H), 1.23 (s, 3 H), 1.04 (s, 3 H); ms *m/z* (M^+) calcd 220.1463, obsd 220.1475. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.37; H, 9.13. Found: C, 75.95; H, 9.08.

5,5-Dimethyl-6,7,8-trihydronaphtho[1,2-b]furan (11). Alcohol (**10**) (128 mg, 0.583 mmol) was dissolved in dry dimethylformamide (3 ml) and pyridinium dichromate (752 mg, 2.0 mmol) was slowly added with cooling in an ice bath under a drying tube. The mixture was stirred at room temperature for 10 h before being diluted with water (20 ml) and extracted with ether (4 x 5 ml). The combined ether layers were washed with brine, dried over magnesium sulfate, and evaporated to give a crude product which upon chromatography (silica gel, elution with 50% ether in hexane) gave **11** (57 mg, 49%); ir (neat, cm^{-1}) 2910, 1460, 1260, 1020, 795, 730; ^1H nmr (90 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.47 (d, J = 2.5 Hz, 1 H), 7.05 (br s, 1 H), 6.55 (dd, J = 2.5, 1 Hz, 1 H), 2.88 (br t, J = 6 Hz, 2 H), 2.0-1.6 (m, 4 H), 1.30 (s, 6 H); *ms m/z* (M^+-CH_3) calcd 200.1201, obsd 200.1222. *Anal.* Calcd for $C_{14}H_{16}O$: C, 83.91; H, 8.32. Found: C, 83.99; H, 8.04.

2,2-Dimethyl-7-oxo-8-oxa-9-(3-furyl)bicyclo[4.3.0]non-1(6)-ene (13). Alcohol (**10**) (102 mg, 0.464 mmol) was dissolved in water and tetrahydrofuran (1:3, 6 ml) and silver(II) oxide[19] (570 mg, 4.6 mmol) was added. The slurry was stirred at room temperature for 41 h before being filtered through a Celite pad. The filter cake was extracted with ether and the combined organic solutions were washed with brine, dried over magnesium sulfate, and evaporated. The crude material was chromatographed (silica gel, elution with 50% ether in hexane) to give **13** (60 mg, 55%); ir (neat, cm^{-1} 2920, 1760, 1640, 1460, 1295, 1150, 945, 900, 722; ^1H nmr (90 MHz, $CDCl_3$) δ 6.20 (m, 1 H), 6.10 (m, 1 H), 5.85 (m, 1 H), 4.10 (br d, J = 13 Hz, 1 H), 3.70 (d, J = 2 Hz, 1 H), 3.42 (dd, J = 13, 6 Hz, 1 H), 2.0-1.4 (m, 4 H), 1.20 (s, 3 H), 1.16 (s, 3 H); ms *m/z* (M^+) calcd 234.1256, obsd 234.1247.

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