A Free Radical Method for Attaching an Oxygen-containing Ring to Either Face of a Bicyclic Structure

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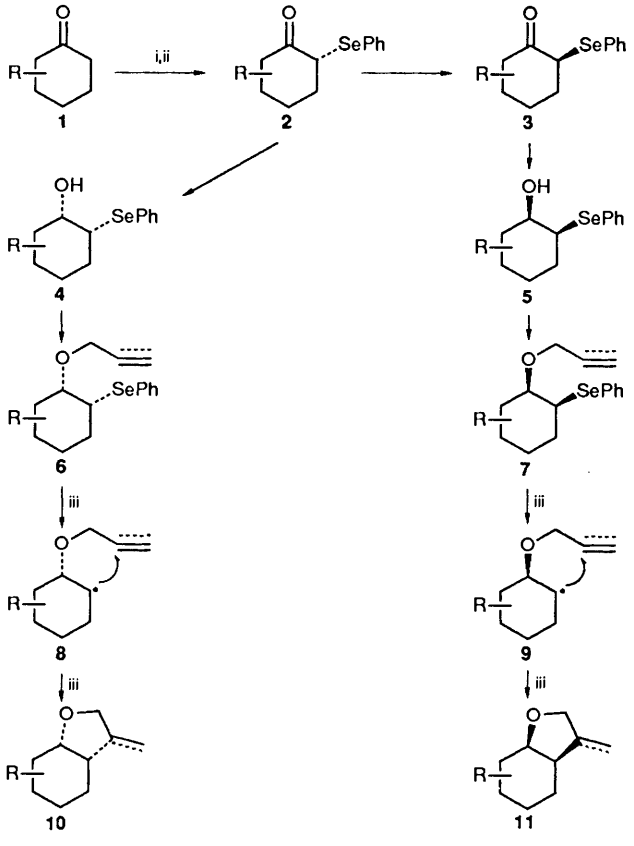
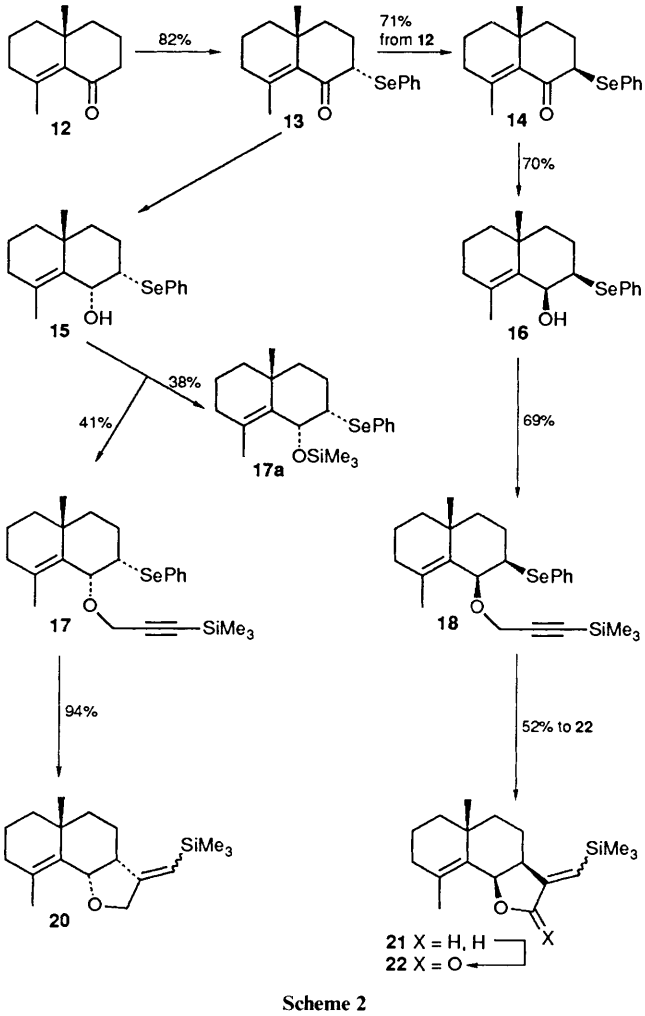
A method is described for attaching an oxygen-containing ring to either face of a cyclic ketone. The procedure involves selenenylation *via* the enolate followed by diisobutylaluminium hydride reduction to afford a *cis* α-(phenylseleno) alcohol. A prop-2-ynyl chain is then attached to the hydroxy group, and radical cyclization generates a new ring. If the original α-(phenylseleno) ketone is deprotonated and reprotonated, the same sequence of reduction, *O*-alkylation, and radical closure then serves to generate a new ring on the other face of the starting ketone.

We report a method for constructing an oxygen-containing ring on either face of an existing cyclic structure. The method, which is illustrated in Scheme 1, uses radical closure, and depends for its implementation on the stereo-electronic and steric factors that control both the reaction of enolates with electrophiles[1] and reduction of the resulting ketones.[2] The procedure can be applied to those ketones **1** that react with benzeneselenenyl chloride (*via* their enolates) from the less hindered face (**1** → **2**). In such cases, deprotonation of the selenide **2** and reprotonation (from the less hindered side) will give the isomeric compound **3**. With both **2** and **3** the bulk of the phenylseleno group should control the steric course of the carbonyl reduction, leading, in the ideal case, to alcohols **4** and **5**, respectively. Attachment, *via* the resulting hydroxy groups, of a pendant with a suitably located π-bond (**4** → **6**, and **5** → **7**) would then set the stage for radical closure, as shown in Scheme 1. In a typical example, where the starting ketone is part of a rigid polycyclic structure, the radical (see **8** and **9**) would have to close onto a pendant that is in either an axial or equatorial conformation if both **10** and **11** are to be accessible. Closure of a cycloalkyl radical onto an unsaturated pendant is, of course, well known, but little information is available on the effect of the conformation (axial or equatorial) of the pendant,[3] especially when the latter is equatorial, and the method of Scheme 1 provides an opportunity to examine this point.[4]



Scheme 1 *Reagents:* i, LDA; ii, PhSeCl; iii, Ph_3SnH

Selenenylation of ketone **12**[5] (Scheme 2) gave the axial selenide **13** (82%). Further treatment with lithium diisopropyl-



Scheme 2

amide (LDA) and reprotonation then afforded the equatorial isomer **14** (71% from **12**).[5] In each case reduction with diisobutylaluminium hydride (DIBAL) gave an alcohol in 70% yield corresponding to formal hydride delivery from the face opposite the phenylseleno group.[6] Attachment of a suitable acetylenic chain was accomplished by treating each alcohol with sodium hydride in the presence 3-bromo-1-(trimethylsilyl)-prop-1-yne.[7] The equatorial alcohol **15** gave the desired product **17** in 41% yield, together with the silyl ether **17a** (38%), while *O*-alkylation of the axial alcohol **16** (to give **18**), was more efficient (69%).[6] The by-product **17a** can be desilylated (91%) with tetrabutylammonium fluoride in THF.

When the selenide **17** was stirred at room temperature with tributyltin hydride and triethylborane[8] the desired cyclized product **20** could be isolated in almost 95% yield as a 1:1 mixture of geometrical isomers. Cyclization of the other selenide **18** was arbitrarily done by slow addition of triphenyltin hydride and azoisobutyronitrile (AIBN) to a refluxing solution of the selenide in benzene.[5] As the aim of that experiment was to prepare the naturally occurring lactone, frullanolide, the initial product **21** was immediately oxidized to **22**, which was isolated in 52% overall yield.[5]

These experiments show that an oxygen-containing ring can be attached to *either* face of a cyclic structure using the principle summarized in Scheme 1. In the case of the equatorial pendant (see **17**) the radical closure is particularly efficient.

Experimental

The same general procedures were used as reported previously.[9] *J*-Values are recorded in Hz.

trans-3,4,4a,5,6,7-*Hexahydro*-4a,8-*dimethyl*-2-(*phenylseleno*)-*naphthalen*-1(2H)-*one* **13**.—A solution of the α,β-enone **12** (178.14 mg, 1 mmol) in dry THF (2 cm^3) was added dropwise during 30 min to a stirred and cooled (−78 °C) solution of LDA [prepared from diisopropylamine (0.231 cm^3, 1.65 mmol) and butyllithium (1.6 mol dm^{-3}, 0.813 cm^3, 1.3 mmol) in THF (4 cm^3)]. The mixture was stirred for a further 1.5 h at −78 °C and benzeneselenenyl chloride (344.7 mg, 1.8 mmol) in THF (1 cm^3) was added in one portion. The cooling-bath was exchanged for one at −30 °C and, after 2 h, the reaction was quenched with glacial acetic acid (0.112 cm^3). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 18 cm) with 4% ethyl acetate–hexane afforded the α-(phenylseleno) ketone **13** (273 mg, 82%) and the β-epimer **14**[5] (46 mg, 14%). The α-epimer **13** was a pale yellow solid, identical with the material obtained previously as a minor by-product in the synthesis of **14**.[5]

1,2,3,4,4a,5,6,7-*Octahydro*-*t*-4a,8-*dimethyl*-c-2-(*phenylseleno*)*naphthalen*-r-1-*ol* **15**.—Diisobutylaluminium hydride (1.0 mol dm^{-3} solution in hexane; 2.65 cm^3, 2.65 mmol) was added dropwise over 20 min to a stirred and cooled (−78 °C) solution of phenylseleno ketone **13** (493 mg, 1.48 mmol) in toluene (17 cm^3). The mixture was stirred for a further 1 h at −78 °C and then methanol (3 cm^3) was added, followed by aqueous acetic acid (50% v/v, 1 cm^3), and the solution was allowed to warm to room temperature. The solvents were evaporated and the residue was extracted with 10% ethyl acetate–hexane (3 × 20 cm^3). The combined organic extracts were washed with water (2 × 20 cm^3), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm) with 5% ethyl acetate–hexane afforded phenylseleno alcohol **15** (350 mg, 70%) as a homogeneous [TLC (silica, 5% ethyl acetate–hexane)], pale yellow oil: ν_{max}/cm^{-1} (FT) ($CHCl_3$ cast) 3470, 1650, 1580, 1477 and 1456; δ_H($CDCl_3$; 300 MHz) 1.07 (3 H, s), 1.24–1.45 (3 H, m), 1.54–1.74 (3 H, m), 1.76 (3 H, s), 1.78–2.15 (3 H, m), 2.18 (1 H, m), 2.48 (1 H, d, *J* 4.5), 3.76 (1 H, dt, *J* 7.5, 3.0), 4.53 (1 H, br dd, *J* 4.5, 3), 7.28 (3 H, m) and 7.58 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) 18.36, 19.49, 25.20, 25.95, 33.26, 33.90, 35.58, 39.75, 50.82, 69.05, 127.52, 129.12, 129.48, 131.75, 134.23 and 135.04 (Found: M^+, 336.1000; C, 64.7; H, 6.95. $C_{18}H_{24}OSe$ requires 336.0993; C, 64.47; H, 7.26%).

Desilylation of 1,2,3,4,4a,5,6,7-*Octahydro*-t-4a,8-*dimethyl*-c-2-(*phenylseleno*)-r-1-(*trimethylsilyloxy*)*naphthalene* **17a**.—Tetrabutylammonium fluoride (1.10 mol dm^{-3} solution in THF; 0.27 cm^3, 0.291 mmol) was added in one portion to a stirred solution of *O*-silyl ether **17a** (79.0 mg, 0.194 mmol) in THF (5 cm^3). The mixture was stirred at room temperature for 30 min [TLC control (silica gel, 5% ethyl acetate–hexane)] and then filtered through a pad of silica gel (2 × 3 cm) with 5% ethyl acetate–hexane. The solvents were evaporated and flash chromatography of the residue over silica gel (2 × 18 cm) with 5% ethyl acetate–hexane yielded the phenylseleno alcohol **15** (59.3 mg, 91%) identical (^1H NMR) with the sample made by DIBAL reduction of phenylseleno ketone **13**.

1,2,3,4,4a,5,6,7-*Octahydro*-t-4a,8-*dimethyl*-c-2-(*phenylseleno*)-r-1-[3-(*trimethylsilyl*)*prop*-2-*ynyloxy*]*naphthalene* **17**.—Sodium hydride (60% dispersion in oil; 59.2 mg, 1.48 mmol) was added in one portion to a stirred solution of phenylseleno alcohol **15** (330 mg, 0.985 mmol) in THF (15 cm^3). The mixture was stirred at room temperature for 45 min and then 3-bromo-1-(trimethylsilyl)prop-1-yne[7] (1.13 g, 5.91 mmol) in THF (7 cm^3) was added rapidly. The resulting mixture was heated at 60 °C for 3.5 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (3 × 18 cm) with hexane afforded the silyl ether **17a** (154.0 mg, 38%). Continued elution with 2% ethyl acetate–hexane afforded the phenylseleno ether **17** (179.0 mg, 41%), which was a colourless, homogeneous [TLC (silica, 2% ethyl acetate–hexane)] oil: ν_{max}/cm^{-1} (FT) ($CDCl_3$ cast) 3050, 2176 and 1656; δ_H($CDCl_3$; 200 MHz) 0.20 (9 H, s), 1.12 (3 H, s), 1.27–2.31 [13 H, series of m (including a singlet at 1.88)], 3.84 (1 H, q, *J* 4.0), 4.17 and 4.30 (2 H, AB system, *J* 16.0), 4.75 (1 H, br s), 7.21–7.32 (3 H, m) and 7.56–7.68 (2 H, m); δ_C($CDCl_3$; 75.47 MHz) −0.11, 18.73, 20.26, 25.62, 27.87, 34.50, 36.46, 37.34, 40.49, 50.75, 56.51, 76.63, 91.28, 102.34, 126.84, 128.85, 130.46, 130.84, 131.49 and 134.13 (Found: M^+, 446.1541. $C_{24}H_{34}OSeSi$ requires 446.1548).

(E)- *and* (Z)-2,3,3a,4,5,5a,6,7,8,9b-*Decahydro*-t-5a,9-*dimethyl*-3-(*trimethylsilylmethylene*)-cis-*naphtho*[1,2-b]*furan* **20**.—A solution of phenylseleno ether **17** (74.0 mg, 0.166 mmol), triethylborane (1.0 mol dm^{-3} solution in hexane; 0.183 cm^3, 0.183 mmol), and tributyltin hydride (53.15 mg, 0.049 cm^3, 0.183 mmol)[8] was stirred at room temperature for 4 h. The solvent was evaporated and flash chromatography of the residue over silica gel (2 × 18 cm) with 2% ethyl acetate–hexane afforded the starting material (13 mg, 17%), the isomer (*Z*)-**20** (17 mg, 35.5%) as a colourless oil and the isomer (*E*)-**20** (19 mg, 39.5%), also as a colourless oil. The (*Z*)-isomer had: ν_{max}/cm^{-1} (FT) ($CDCl_3$ cast) 1640; δ_H($CDCl_3$; 300 MHz) 0.08 (9 H, s), 1.00 (3 H, s), 1.23–1.40 (3 H, series of m), 1.45–1.64 (3 H, series of m), 1.65–1.85 [4 H, series of m (including a singlet at 1.77)], 1.87–2.16 (3 H, m), 2.74–2.84 (1 H, m), 4.23 (1 H, ddd, *J* 13.5, 2.2, 1.0), 4.33 (1 H, dt, *J* 13.5, 2.0), 4.61 (1 H, d, *J* 5.2) and 5.39 (1 H, q, *J* 1.8); δ_C($CDCl_3$; 75.47 MHz) −0.46, 18.76, 19.82, 23.54, 25.95, 33.11, 35.13, 39.04, 44.63, 68.67, 77.47, 115.91, 132.18, 132.32 and 163.64 (two signals are coincident in this spectrum) (Found: M^+, 290.2071. $C_{18}H_{30}OSi$ requires 290.2076).

The (*E*)-isomer had: ν_{max}/cm^{-1} (FT) ($CDCl_3$ cast) 1640; δ_H($CDCl_3$; 300 MHz) 0.14 (9 H, s), 1.01 (3 H, s), 1.29 (4 H, series of m), 1.55–1.69 [4 H, series of m (including a singlet at

1.72)], 1.92–2.21 (3 H, series of m), 2.88 (1 H, br quin, *J* 5.0), 4.15 (1 H, dd, *J* 13.5, 1.5), 4.43 (1 H, br dt, *J* 13.5, 1.5), 4.49 (1 H, d, *J* 4.2) and 5.21 (1 H, q, *J* 1.0); $\delta_C(CDCl_3$; 75.47 MHz) 0.04, 18.61, 19.17, 24.38, 25.55, 31.84, 32.21, 34.70, 38.45, 39.03, 71.39, 77.61, 115.55, 132.47, 133.65 and 164.76 (Found: M^+, 290.2067. $C_{18}H_{30}OSi$ requires 290.2061). A second run was done (reaction time: 1.5 h) on 2.3 times the above scale. A mixture of both isomers in a 1:1 ratio (^1H NMR) was obtained in 94% yield.

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