Anomalous Reactivity of Sodium Phenyl Selenide

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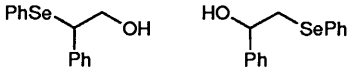
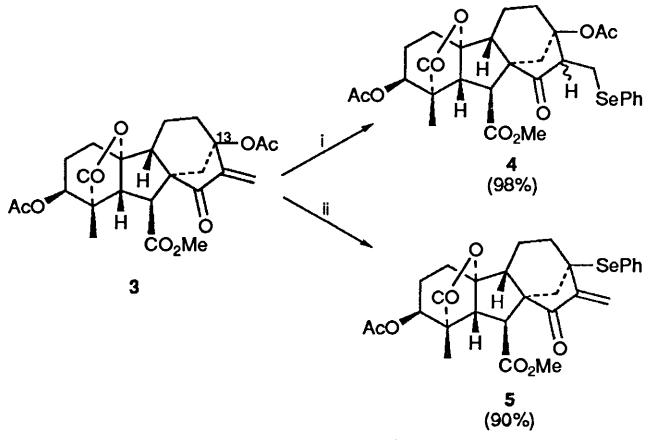
Reaction of sodium phenyl selenide generated from benzeneselenol–sodium hydride–tetrahydrofuran with the enone **3** gives the expected conjugate addition product **4** whereas the reagent prepared from diphenyl diselenide–sodium metal–tetrahydrofuran/ultrasound leads to substitution of the bridgehead 13-acetate in **3** to give the 13-phenyl selenide **5**. Experimental results for this unexpected observation are in accord with the proposal that the reaction may proceed *via* an 'anti-Bredt' bicyclo[3.2.1]octenone intermediate.

The synthetic utility of PhSe anions for effecting a range of transformations, including nucleophilic addition to epoxides, halides and enones as well as S_N2-type cleavages of alkyl esters is now well established.[1] Several methods for the generation of PhSe anions have been described including reaction of diphenyl diselenide with: (i) sodium metal in tetrahydrofuran (THF) with low intensity ultrasound,[2] (ii) sodium borohydride in ethanol[3] and (iii) tributylphosphine in THF then aqueous sodium hydroxide.[4] Alternatively, sodium phenyl selenide may be prepared from benzeneselenol using sodium hydride in THF.[5] In a few cases, it has been reported that the reactivity of sodium phenyl selenide is dependent upon the method of generation of the anion. For example, the regiochemistry of ring opening of styrene oxide varies depending upon the source of the anion: PhSeSePh/Bu_3P/NaOH gives a mixture of the primary alcohol **1** and the secondary alcohol **2**[4] whereas PhSeSePh/Na gives



1 **2**

solely the secondary alcohol **2**.[2] We now report that the source of the PhSe anion has a profound effect on its reactivity with the gibberellin enone **3** giving either the conjugate addition product **4** or substitution of the bridgehead acetate by PhSe to give **5** (Scheme 1). The reasons for this contrasting reactivity have been investigated and a mechanism for the unexpected bridgehead substitution is proposed.



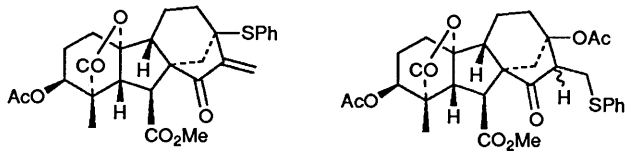
3 **4** (98%) **5** (90%)

Scheme 1 *Reagents and conditions:* i, PhSeH/NaH; ii, either PhSeSePh/Na/ultrasound or PhSeSePh/$NaBH_4$

Two methods were initially examined for the reaction of the enone **3** with sodium phenyl selenide. *Method A*. Treatment of benzeneselenol with sodium hydride[5] gave a grey suspension which was transferred to a solution of the known enone **3**[6] at room temperature. *Method B*. Treatment of diphenyl diselenide with sodium metal under ultrasonic conditions as described by Ley *et al.*[2] gave a cream suspension which was transferred to a solution of the enone **3** at room temperature.

In each case a single product was obtained. Method A gave the expected conjugate addition product **4** (Scheme 1). In contrast Method B gave **5** in which the bridgehead 13-acetate had been replaced by PhSe; interestingly, other functionalities within the molecule were unaffected. Similarly, reaction of the enone **3** with the reagent generated from diphenyl diselenide and sodium borohydride[3] led to substitution of the bridgehead 13-acetate **5**.† *From the results it is evident that the reagents generated by Method A and Method B must be different.*

Analogous results were observed on reaction of sodium phenyl sulfide with the enone **3**. The reagent prepared from diphenyl disulfide with either sodium metal/ultrasound or with sodium borohydride gave the 13-thioether derivative **6** (53% yield) whereas the thiolate anion generated from thiophenol and sodium hydride gave the expected conjugate addition product **7** (75% yield).



6 **7**

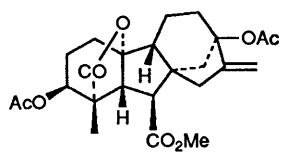
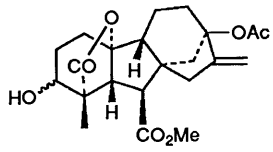
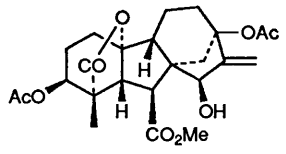
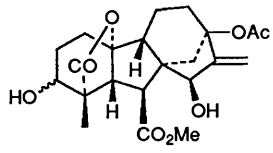
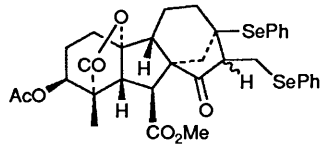
The mechanism of substitution of the bridgehead 13-acetate is particularly intriguing since other potentially reactive functionalities within the molecule remain intact. It seems most unlikely that the reaction is proceeding *via* an S_N2-type ester cleavage with either a selenolate or thiolate anion since the 7-methyl ester and secondary acetate are unaffected.‡ Therefore, a series of experiments were conducted to probe the mechanism of substitution of the bridgehead acetate in the bicyclo[3.2.1]octenone **3**; the results are summarised in Table 1.

Entries (i) and (ii) reveal that the 15-carbonyl is necessary for bridgehead substitution to occur. Entry (iii) shows that reaction of the 13-phenylseleno derivative **5** with the reagent generated

† All compounds were characterised by ^1H and ^{13}C NMR, EI mass spectrometry, and microanalysis and/or high resolution mass spectrometry.

‡ NaSpr/HMPA has been widely used in the gibberellin field to convert 7-methyl esters cleanly into the corresponding free acids, *e.g.* M. Penny and C. L. Willis, *J. Chem. Soc., Chem. Commun.*, 1993, 1111.

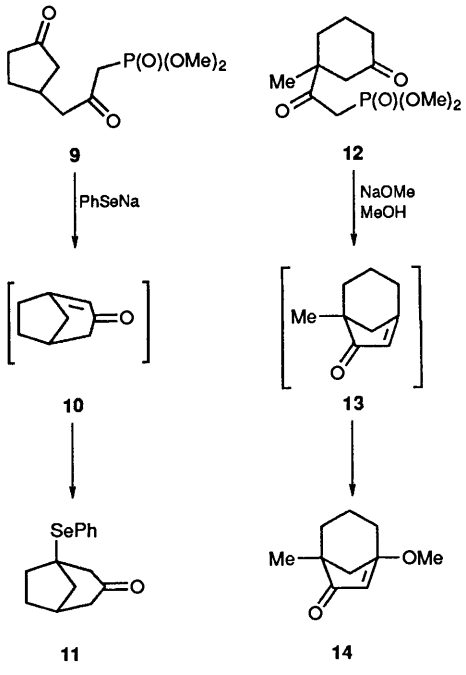
Table 1

Entry	Substrate	Method of generation PhSeNa	Product
(i)		B	 (53%)
(ii)		B	 (88%)
(iii)	**5**	A	 **8** (98%)
(iv)	**4**	B	**5** (34%)

by Method A gives the addition product at C-17 to yield **8**. More interestingly, the 13-acetoxy-17-phenyl selenide **4** (entry iv) prepared from the enone **3** by Method A, not only gave the bridgehead substitution on treatment with the reagent from Method B, but also led to regeneration of the exocyclic olefin to give **5** as the sole product.

House *et al.*[7] have reported that bicyclo[3.2.1]oct-1-en-3-one **10** may be transiently formed from the diketo phosphonate **9** and trapped by addition of nucleophiles such as PhSe (generated by PhSeSePh/$NaBH_4$) to give the keto selenide **11** (Scheme 2). Similarly, the diketone **12** reacts with sodium methoxide to give the methyl ether **14**. The results of our substitutions may be rationalised in terms of the formation of an analogous strained bridgehead enone **15** as shown in Scheme 3. Thus, conjugate addition of the selenide followed by elimination of the 13-acetate gives **15**, analogous to **13** proposed by House. Intermolecular attack by further PhSe at C-13 in **15** and regeneration of the exocyclic olefin (*viz.* entry iv, Table 1) gives the observed product **5.**

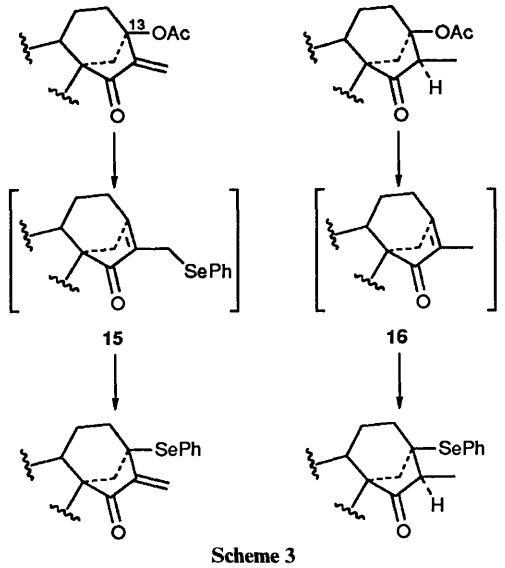
The reactivity of further substrates with 'sodium phenyl selenide' was then examined. The saturated ketone **17**, prepared from the enone **3** with zinc in acetic acid, was treated with the reagent generated by Method B (Scheme 4). A single product **18** was obtained in which the 13-acetate had been replaced by a PhSe group. This reaction may also be envisaged as proceeding *via* a strained bridgehead enone formed by abstraction of the acidic 16-hydrogen (Scheme 3). Conjugate addition by PhSe at C-13 in **16** would then give the observed product **18**. This mechanism is in accord with the results of the two further experiments. Firstly, reaction of the 16,17-dideuterio ketone **19** (Scheme 4) with sodium phenyl selenide generated by Method B gave the expected 13-phenylseleno derivative **20** with hydrogen, not deuterium, at C-16. However, the possibility that the 16-deuterium was lost simply through exchange under the reaction



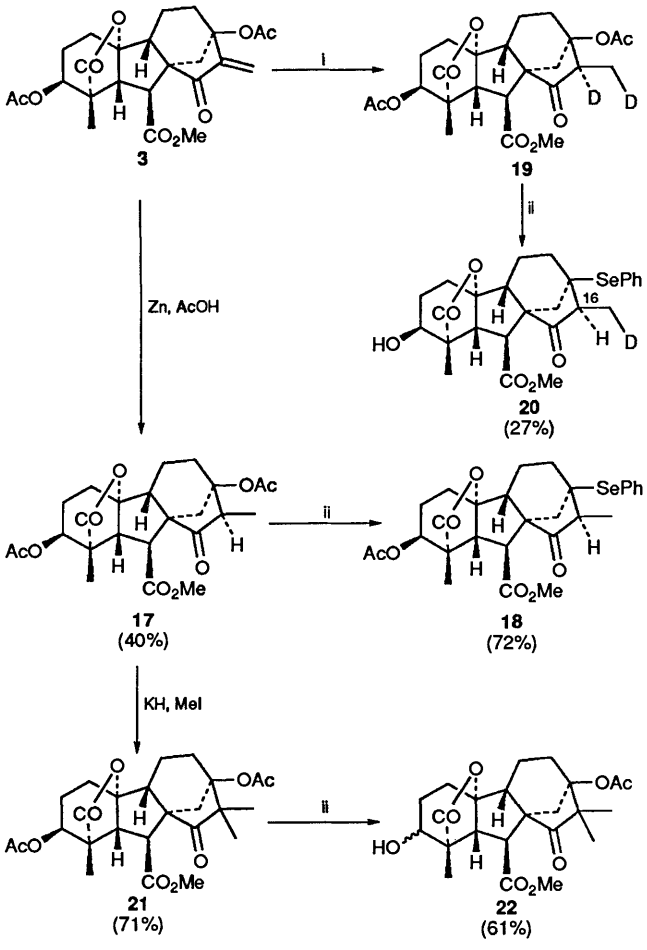
Scheme 2

conditions cannot be ruled out. Secondly, the 13-acetoxy-16,16-dimethyl ketone **21**, prepared from the saturated ketone **17** with potassium hydride and methyl iodide, returned the 13-acetoxy derivative **22** on reaction with sodium phenyl selenide, Method B. Formation of the 13,16-double bond is obviously impossible in the case.

From the unexpected results reported in this communication,



Scheme 3



Scheme 4 *Reagents and conditions:* i, Zn, CD_3CO_2D; ii, PhSeSePh, Na, ultrasound; iii, Zn/AcOH; iv, KH, MeI

it is evident that the method of generation of 'sodium phenyl selenide' can have a profound effect on the outcome of a reaction. One explanation for the observed differences in reactivity is that the 'sodium phenyl selenide' formed by Method B (PhSeSePh/Na/THF/ultrasound) is radical in nature, whereas the reagent from Method A (PhSeH/NaH/THF) is ionic. Further investigations will be undertaken to test the validity of this hypothesis as well as to confirm the proposed mechanism of substitution of the bridgehead 13-acetate by PhSe.

Experimental

Typical Procedure.—Method A. Sodium hydride (60% dispersion in oil; 10 mg, 0.4 mmol) pre-washed with light petroleum, 18-crown-6 (10 mg) and CH_2Cl_2 (5 cm^3) were stirred under a nitrogen atmosphere at room temperature. Benzeneselenol (0.03 cm^3, 0.26 mmol) was added dropwise to form a grey–green solution. 15-OxoGA$_1$ methyl ester diacetate **3** (60 mg, 0.11 mmol) in CH_2Cl_2 (5 cm^3) was added to the reaction mixture which was then stirred at room temperature for 5 h. The reaction mixture was worked up by dilution with water, acidification to pH 2 with 2 mol dm^{-3} HCl and extraction with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated under reduced pressure and the crude product was purified by column chromatography. Elution with 35% ethyl acetate in light petroleum gave **4** (60 mg), m.p. 170 °C (from ethyl acetate–light petroleum) (Found: C, 58.25; H, 5.3. $C_{30}H_{34}O_9Se$ requires C, 58.35; H, 5.51%); $\delta_H(CDCl_3)$ 1.02 (s, 18-H$_3$), 1.99 and 2.08 (2 × s, 3- and 13-OAc), 2.54 (d, *J* 10.5,* 6-H), 2.94 (m, 17-H$_2$), 3.11 (d, *J* 11.5, 14-H), 3.21 (d, *J* 10.5, 5-H), 3.60 (s, CO_2CH_3), 4.9 (br s, 3-H) and 7.2 (m, SePh); $\delta_C(CDCl_3)$ 14.7 (C-18), 17.2 (C-11), 21.0 and 21.3 (2 × $OCOCH_3$), 25.4 and 26.9 (C-1 and C-2), 37.4 (C-12), 47.5 (C-14), 49.5 (C-8), 50.6 (C-9), 51.5 and 52.0 (C-5 and C-6), 53.6 (C-4), 71.0 (C-3), 82.9 (C-13), 92.7 (C-10), 126.9, 129.0, 130.6, 131.3, 132.1 and 132.3 (SePh), 169.9 (C-7), 170.1 and 171.0 (2 × $OCOCH_3$), 176.2 (C-19) and 214.1 (C-15); *m/z* 634 (M^+, 4%), 560 (3), 532 (6), 460 (11), 429 (46), 372 (6), 312 (73), 268 (11), 234 (54), 154 (100) and 77 (69).

Method B. Sodium (50% dispersion in oil; 50 mg, 2.09 mmol) was washed with light petroleum and benzophenone (10 mg) and THF (1 cm^3) were added to it; the mixture was then sonicated until a deep blue colour developed (5 min). Diphenyl diselenide (150 mg, 0.479 mg) in THF (2 cm^3) was added to the reaction mixture which was then sonicated for 1 h. The reagent so prepared was added to the enone **3** (217 mg, 0.417 mmol) and the reaction mixture stirred for 18 h at room temperature. A work-up procedure similar to that described above gave the crude product which was purified by column chromatography. Elution with 35% ethyl acetate in light petroleum gave **5** (200 mg), m.p. 237 °C (from ethyl acetate–light petroleum) (Found: C, 60.1; H, 5.6. $C_{28}H_{30}O_7Se$ requires C, 60.22; H, 5.73%); $\delta_H(CDCl_3)$ 1.10 (s, 18-H$_3$), 2.15 (s, OAc), 2.37 (d, *J* 11.5, 14-H), 2.55 (d, *J* 10.5, 6-H), 3.28 (d, *J* 10.5, 5-H), 3.52 (s, CO_2CH_3), 4.97 (br s, 3-H), 5.83 and 6.24 (2 × s, 17-H$_2$) and 7.3 (m, SePh); $\delta_C(CDCl_3)$, 14.9 (C-18), 18.3 (C-11), 21.1 ($COCH_3$), 25.3, 27.2 and 37.1 (C-1, C-2 and C-12), 39.2 (C-14), 48.0 (C-8), 48.4 ($COOCH_3$), 49.4, 51.1 and 51.6 (C-5, C-6 and C-9), 53.7 (C-4), 59.9 (C-13), 71.1 (C-3), 93.0 (C-10), 120.7 (C-17), 126.8, 129.0, 137.3 (SePh), 151.5 (C-16), 170.2 (C-7), 171.2 ($OCOCH_3$), 176.5 (C-19) and 202.5 (C-15); *m/z* 558 (M^+, 100%), 281 (25), 269 (90), 209 (49), 91 (45) and 43 (38).

Acknowledgements

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* *J* Values in Hz.

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