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Hydroxyselanylation of acyloxycyclohex-3-enes

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Abstract—In contrast to the corresponding hydroxyiodination reactions, the reaction of acetoxycyclohex-2-ene **1** with *N*-PSP in the presence of water shows little regiocontrol, but is highly diastereoselective. However, the same reaction of the (*R*)-phenylglycinate derivative of (±)-cyclohexen-3-ol is highly diastereoselective, *and* regioselective. A hydrogen-bonding interaction is proposed to rationalize these differing selectivities.

1. Introduction

We have previously described our studies on the reactions of acyloxycyclohexenes (such as **1** and **2**, Scheme 1) with iodinating agents.[1] Thus, these alkenes react under a range of conditions in the presence of water and an iodonium source, to give *trans*-1,2-hydroxyiodides, often with excellent regio- and stereocontrol; we have used this reaction in an iterative manner to prepare tetraacetylconduritol D **3** (Scheme 1).[2]

We have also reported[3] that phenylselanylation of **1** is diastereoselective but not regioselective, in stark contrast to the highly selective hydroxyiodination process, but the hydroxyselanylation reaction is intimately related to the structure of the acyl group: phenylglycinates analogous to **1** undergo reaction with *N*-PSP with excellent stereo- *and* regiocontrol.[4] We report here in full the data arising from these hydroxyselanylations, with a comment on the underlying mechanistic features of the processes.

2. Results and discussion

2.1. Hydroxyselanylation of acetoxycyclohex-3-ene

Thus, we had previously observed that hydroxyiodination of **1** proceeded to give a single adduct, **4**, on small scale and an additional regioisomeric monoacetate **5** in larger scale reactions (Scheme 2). This confirmed our postulate that the acetate group was providing anchimeric assistance in the addition of oxygen to the alkene: only by invoking dioxolonium ion **6** (derived from the corresponding α-iodonium ion) one could rationalize the obtention of isomers.

This observation contrasted with the similarly diastereo- and regioselective addition of phenyselanyl chloride to **1**, which Liotta et al. reported to give a single regio- and stereoisomer **7**, arising from a β-selanonium ion.[5] NMR studies by Cooper and Ward[6] later revealed that **7** was accompanied by a small amount of a diastereomer, **8** (Scheme 3). Presumably, in this case, any influence of the carbonyl lone pair is confined to an electrostatic interaction with the selenium positive charge.

Thus, we were intrigued to observe the reaction of **1** with selanylating reagents in the presence of water. In our initial studies, we exposed **1** to PhSeCl, in chloroform containing a few drops of water, whereupon we isolated only chloroselanide **7**, but these reactions were inefficient (starting material was never fully consumed in the processes) and often difficult to purify.[†] We turned our attention to an alternative electrophilic selanylating reagent, *N*-PSP,[7] and found that reaction with **1** in the presence of 1 equiv of camphor sulfonic acid was a much smoother process. From the reaction, isomeric hydroxyselanides **9** and **10** were isolated in good yield and in ~50:50 ratio (Scheme 4). We identified CSA as the source of water by carrying out the reaction in the presence of molecular sieves, whereupon starting material was recovered unchanged from the reaction; thus we added a few drops of water[8] to subsequent reactions.

[†] Cooper and Ward subsequently reported (op. cit.) that similar reactions using a larger excess of water gave **9** and **10** instead of **7** (85% yield, ~50:50 ratio), indicating that concentration effects exert a powerful influence upon the reaction.

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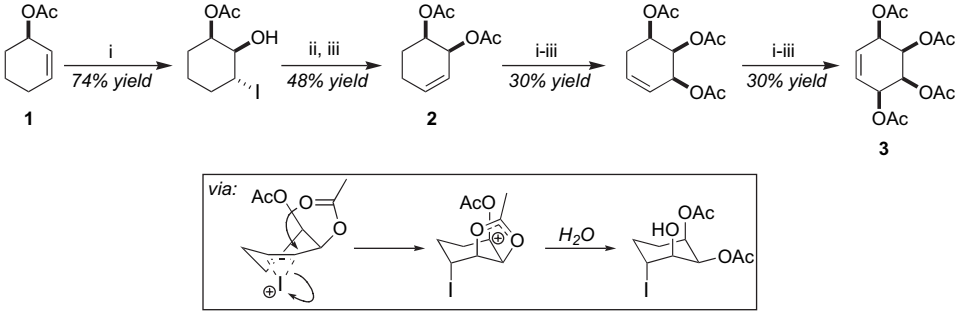
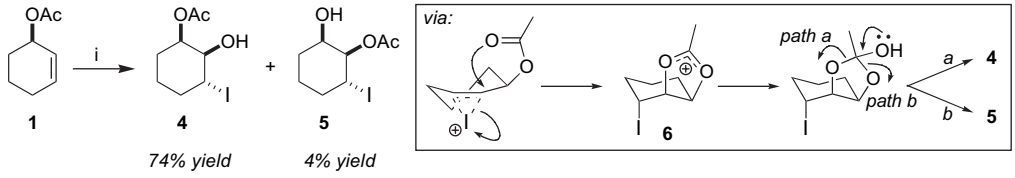
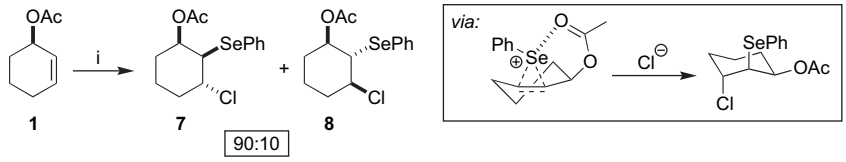


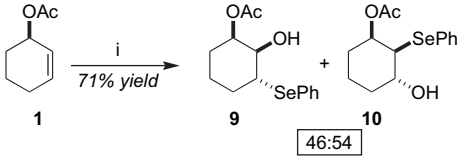
Scheme 1. *Reagents*: (i) *N*-iodosuccinimide, water, MeCN; (ii) Ac_2O, pyridine, DMAP; (iii) DBU, toluene, reflux.



Scheme 2. *Reagents*: (i) *N*-iodosuccinimide, water, MeCN.



Scheme 3. *Reagents*: (i) PhSeCl, *d*-chloroform.



Scheme 4. *Reagents*: (i) *N*-phenylselanylphthalimide (2 equiv), CSA, room temperature.

The regio- and stereochemical assignments, based on the observed coupling constants for the downfield resonances, were straightforward (Fig. 1).

Under a wide range of different conditions, the **9/10** ratio was unchanged; we next examined the effect of substitution at the acetate subunit, by carrying out the hydroxyselanylation on phenylacetate **11**.[‡] This compound was hydroxyselanylated in a slightly better yield, to give hydroxyselenides **12** and **13** (Scheme 5): however, these compounds were not easily separable chromatographically. By analogy with the chemical shifts observed for the acetate analogues, the ratio **12/13** was judged to be ~50:50, paralleling to that seen in the reaction of **1**.

To confirm this tentative analysis, **12** and **13** were deselanylated under thermolytic conditions, to give the corresponding monoesters **14** and **15**, which were easily separated by flash chromatography. Analysis of the ^{1}H NMR spectra for the monoesters confirmed the original assignments.

Compound **14** was then prepared unambiguously by a sequential hydroxyiodination–reductive deiodination process: **11** reacted under typical hydroxyiodination conditions (vide supra) to give hydroxyiodide **16**, as a single product (Scheme 6). Thermolytic reduction again gave **14**, and we were able to confirm the original structural assignment.

Finally in this series of compounds, we performed a rigorous chemical correlation. Thus, the acetoxy compounds **9** and **10** were reductively dechalcogenated: **9** gave (±)-*cis*-1-acetoxy-2-hydroxycyclohexane **17**,[9] directly (Scheme 7).

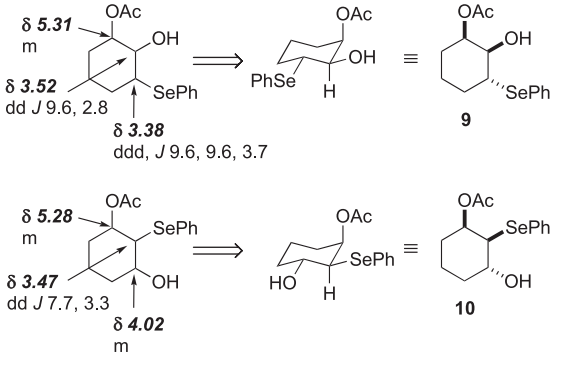
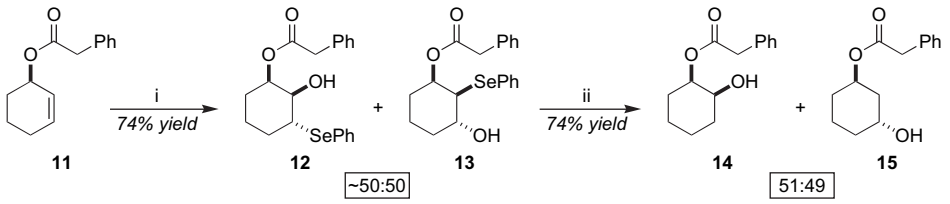
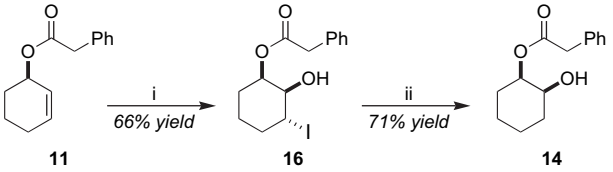


Figure 1.

[‡] Other esters did not react cleanly in these additions; we are currently investigating the reasons for this observation.



Scheme 5. *Reagents*: (i) *N*-phenylselanylphthalimide, CSA, water, room temperature; (ii) Bu_3SnH, AIBN, PhH, reflux.



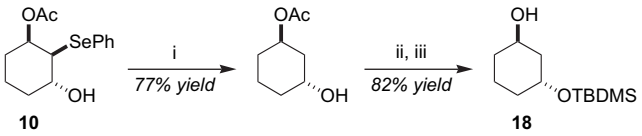
Scheme 6. *Reagents*: (i) *N*-iodosuccinimide, water, CH_2Cl_2; (ii) Bu_3SnH, AIBN, PhH, reflux.

^{1}H decoupling experiments confirmed the cis-arrangement in this molecule.

Upon deselanylation (Scheme 8), **10** gave (±)-*trans*-1-acetoxy-3-hydroxycyclohexane, which was converted in two steps to (±)-*trans*-3-hydroxy-1-(*tert*-butyldimethylsilyl)oxycyclohexane **18**, previously prepared by Evans et al.[10]

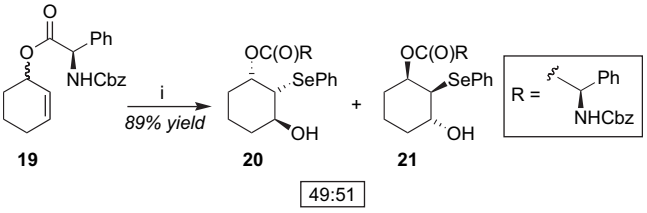
2.2. Hydroxyselanylation of (phenylglycinoyl)oxycyclohex-3-ene

Having seen no dominant acetate directing effect on these hydroxyselanylation processes, and being cognizant of the known effects of hydrogen-bonding upon selanylation reactions,[4,5] we next sought to introduce an H-bonding component into the acyl substituent. Since we eventually required access to the single enantiomers of some of the hydroxyselenides and iodides from these reactions, we chose to use a chiral H-bonding acyl species and (primarily for the relatively simple NMR spectra of such compounds) settled upon the (*R*)-phenylglycinoyl substituent. Thus, phenylglycinoate **19**, prepared as an inseparable 1:1 mixture of diastereomers (by reaction of the DBU salt of *R*-phenylglycine with (±)-bromocyclohex-3-ene), was reacted with *N*-PSP in the presence of water. In addition to observing the effect of the branched acyl substituent pattern, we were also keen to ascertain whether or not the asymmetric centre of the side chain would effect a *kinetic resolution*, favouring one

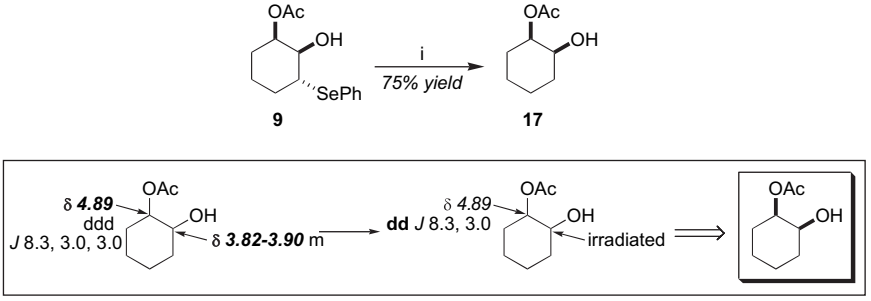


Scheme 8. *Reagents*: (i) Bu_3SnH, AIBN, PhH, reflux; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (iii) $LiOH\cdot H_2O$, THF/H_2O (8:1, reflux).

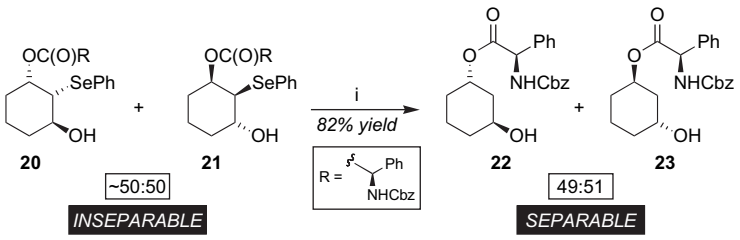
of the absolute configurations of the cyclohexenyl substituent over the other. In fact the reaction proceeded to give roughly equal amounts of two hydroxyselanides, in improved yields compared to the corresponding acetate and phenylacetates (Scheme 9). The process was complicated by the fact that the two products could (except on small scale) be chromatographically separated only with difficulty, but it quickly became apparent that the two products were diastereomers, *not* regioisomers; the compounds were again obtained in roughly equal amounts. Thus, in contrast to the acetate reactions, it seemed that each of the two diastereoisomeric esters had a preference for a *single selenonium ion*, since it is the structure of the selenonium ion, which controls the course of the reaction (assuming the process proceeds by trans-diaxial ring-opening). By analogy with the data collected from previous products, we tentatively assigned structures **20** and **21** to the products of the phenylglycinate reaction.



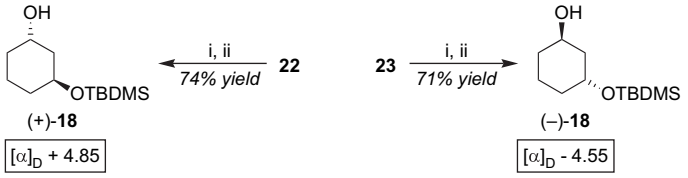
Scheme 9. *Reagents*: (i) *N*-phenylselanylphthalimide, CSA, water, room temperature.



Scheme 7. *Reagents*: (i) Bu_3SnH, AIBN, PhH, reflux.



Scheme 10. *Reagents*: (i) Bu_3SnH, AIBN, PhH, reflux.



Scheme 11. *Reagents*: (i) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (ii) $LiOH \cdot H_2O$, THF/H_2O (8:1, reflux).

Faced with the inability to separate diastereomers **20** and **21**, we carried out a chemical correlation process analogous to that described above for the phenylacetate adduct: **20** and **21** were protiodeselanylated to give hydroxyesters **22** and **23** (Scheme 10). The latter compounds were now easily separated by chromatography and analysis of the associated ^1H NMR spectra supported the original structural assignment we had made for **20** and **21**.

To confirm that only two diastereoisomers were present, we next prepared chiral derivatives of the separated deselenated products. Thus, **22** ($[\alpha]_D$ −31.96) and **23** ($[\alpha]_D$ −41.02) were converted into the corresponding (*R*)-MTPA esters, and analyzed by chromatography and NMR. Frustratingly, the compounds could not be completely separated by any chromatographic means, though ^1H NMR did indicate that single enantiomers (≥90%) were present in each of the MTPA esters. However, despite this disappointing diversion, we still had available to us the chemical correlation applied for (±)-**18**: thus, sequential silylation and hydrolysis of **22** and **23** gave (+)-**18** and (−)-**18**, respectively. Gratifyingly, the specific rotation of each compound was of the same magnitude, within experimental error (Scheme 11).

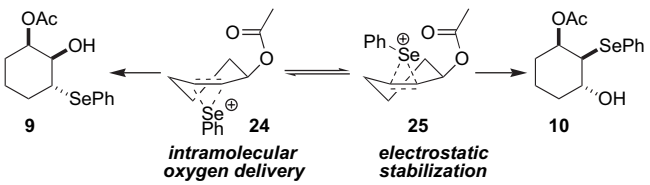
Thus, it was shown that hydroxyselanylation of cyclohexenyl phenylglycinates is *regiospecific* (only 3-hydroxy-2-phenylselanyl products were obtained), and that the reactions are highly *diastereo*selective (each diastereomer of the starting material give only one hydroxyselanide product). There is, therefore, an inherently high face selectivity: the selenium electrophile is delivered only from the β-face of the alkene, *syn* to the acyloxy substituent. The mechanistic features of the reaction are discussed below.

2.3. Mechanistic discussion

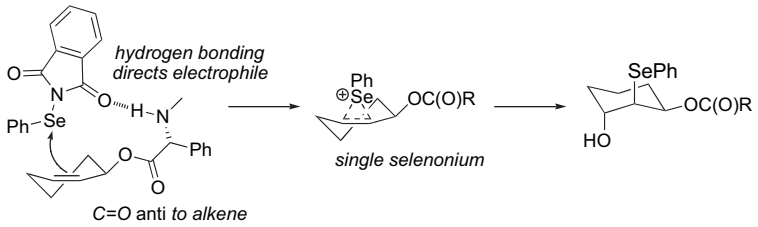
It is well-known that addition reactions of cyclohexenes often proceed via apparently less stable intermediates, under Curtin–Hammett[11] control, due to the low energy barrier for interconversion between the available half-chair conformers. In the case of **1**, the product profile indicates that reaction with *N*-PSP gives equal amounts of both possible selenonium ions, **24** and **25**; these undergo trans-diaxial ring-opening to give hydroxyselenides **9** and **10**, respectively (Scheme 12). The fact that roughly equal amounts of these isomers are obtained implies *the formation of selanonium ion is rate-determining*; ion **24** can undergo intramolecular ring-opening (as seen in the corresponding hydroxyiodination process, Scheme 2), whereas ion **25** experiences an electrostatic effect (cf. the Liotta reaction, Scheme 3), but neither of the latter processes affect the overall course of the reaction. This implies, in turn, that iodination of **1** is controlled by the ring-opening of the iodonium intermediate, and that formation of iodonium is *reversible*, which is well-precedented.

Given that increased steric bulk in the acyl unit does not affect the course of the reaction (Scheme 5), it seems unlikely that the rate-limiting step involves dissociation of the N–Se bond: if such a process was in operation, one would reasonably predict a larger ester group to have more steric repulsions with the relatively bulky phthalimido subunit, leading to a preference for (presumably) the α-selenonium intermediate. No discernable improvement in regioselectivity is observed in the reaction of phenylacetate **11**, again implying that the formation of selenonium is the rate-determining step.

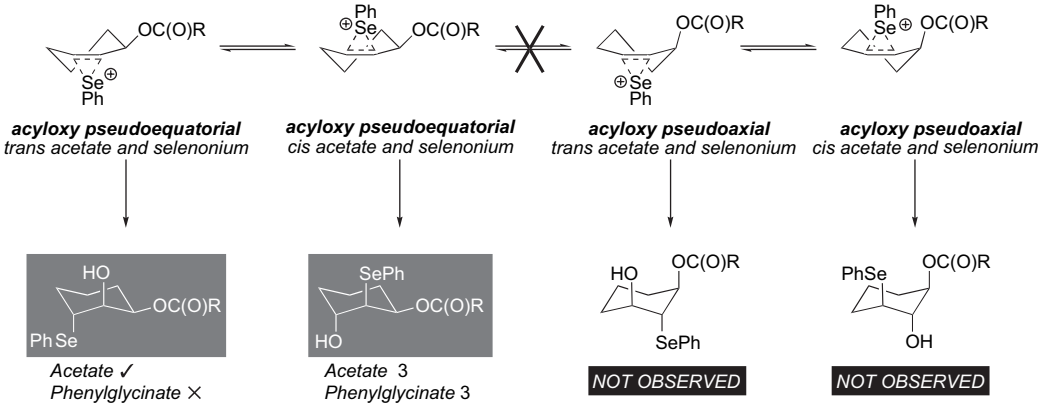
The reaction of the phenylglycinate **19** is surprising, against this mechanistic background. Each diastereomer forms a *single selenonium ion*, where the selenium is located *syn* to the acyloxy substituent (Scheme 13); trans-diaxial ring-opening gives **20** and **21** and in this case there is no intramolecular ring-opening by the acyl oxygen. This implies immediately that the asymmetric centre of the acyl side chain *does not have any influence upon the stereoselectivity of*



Scheme 12.



Scheme 13.



Scheme 14.

the reaction: both diastereomers react in roughly the same yield and with high levels of stereoselectivity.[§] The only other significant structural difference in this acyl group, which can influence the reaction is the N–H bond: we assume, therefore, that formation of selanonium is again rate-determining but now *hydrogen-bonding delivers the selenium electrophile* to the *syn*-face of the alkene (Scheme 13).

Though further study is needed to confirm the hypotheses, we can tentatively predict the preferences for these acyloxy cyclohexenes as follows (Scheme 14): upon reaction with *N*-PSP, simple acyl moieties cannot influence the course of the reaction, because the rate-determining step is formation of the selanonium ion. Only two of the four possible conformers are in operation, those in which the acyloxy substituent is *pseudo*equatorial. Hydrogen bond donors in the acyl group are likely to direct the incoming electrophiles to form β-selanonium ions. Asymmetry present adjacent to the H-bond has no influence upon the course of the reaction, and only *one* of the four possible conformers is of importance.

3. Conclusion

In summary, we have found that hydroxyselanylation of acyloxycyclohexenes can be a highly diastereoselective process, when the acyl substituent contains an H-bond donor. We are currently exploring the scope of these processes and carrying out a detailed study on the mechanistic factors responsible for these phenomena.

[§] When a single equivalent or substoichiometric amount of *N*-PSP is used in the reaction, kinetic resolution has, to date, not been observed; yields are merely diminished.

4. Experimental section

4.1. General techniques

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[12] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether was distilled from sodium benzophenone ketyl; dichloromethane from calcium hydride. Other chemicals were purchased from Aldrich Chemical Co. and purified prior to use, or prepared by literature methods.

Melting points were recorded on either a Kofler hot-stage apparatus and are corrected, or an Electrothermal melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin–Elmer 881 spectrophotometer. Mass spectra were recorded on a Fisons Autospec spectrometer or a VG 9090 mass spectrometer. NMR spectra were carried out on JEOL PMX 60, GX 270, GX 400 or GX 500 spectrometer using tetramethylsilane, chloroform, dichloromethane or acetone as an internal standard. Chemical shifts in ^{1}H NMR spectra are expressed in parts per million downfield from tetramethylsilane, and, in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (*J*) are quoted in hertz.

Reactions involving chemicals or intermediates sensitive to air and/or moisture were conducted under a nitrogen or argon atmosphere in flame- or oven-dried apparatus. Column chromatography was performed using Merck Kieselgel 60 or Fluka Kieselgel 60 silica gel. Analytical thin layer chromatography was carried out using either precoated Merck Kieselgel 60 F_{254} glass-backed plates, or precoated Merck

Kieselgel 60 F_{254} aluminium backed plates and were visualized under UV at 346 nm by staining with iodine and an acidic ammonium molybdate stain (20% w/v ammonium molybdate(VI) tetrahydrate in 10% sulfuric acid).

4.2. (±)-1,2-*trans*-2,3-*cis*-3-Acetoxy-2-hydroxy-1-phenselanylcyclohexane 9 and (±)-1,2-*cis*-2,6-*trans*-2-acetoxy-6-hydroxy-1-phenselanylcyclohexane 10

Acetoxycyclohex-2-ene **1** (140 mg, 1 mmol), *N*-phenylselanylphthalimide (604 mg, 2 mmol), (±)-camphor-10-sulfonic acid (232 mg, 1 mmol), water (3 drops) and dichloromethane (30 ml) were combined and stirred at room temperature for 17 h. The white precipitate, which had formed was filtered and washed with dichloromethane. The combined filtrate and washings were evaporated in vacuo to give a pale yellow solid. Flash column chromatography (ether/petrol, 1:1) yielded **9**, as a colourless solid (103 mg, 33%). ν_{max} (CCl_4)/cm^{-1} 3350, 1721, 1572, 1470; δ_H (270 MHz; $CDCl_3$) 1.38–2.20 (6H, m), 2.11 (3H, s), 2.76 (1H, br s), 3.38 (1H, ddd, *J* 9.6, 9.6 and 3.7), 3.52 (1H, dd, *J* 9.6 and 2.8), 5.28–5.34 (1H, m), 7.24–7.38 (3H, m), 7.58–7.64 (2H, m); δ_C (67.5 MHz; $CDCl_3$) 170.66, 136.15, 134.24, 129.02, 128.23, 72.29, 71.81, 46.28, 31.36, 28.24, 21.24, 20.92 (2×CH_2); *m*/*z* 314 (M^+, 23.7%), 157 (67.7), 147 (60.1), 104 (31.7), 97 (77.6), 43 (100). Hydroxyselenide **10** was also obtained as a colourless solid (120 mg, 38%). ν_{max} (CCl_4)/cm^{-1} 3335, 1717, 1599, 1465; δ_H (270 MHz; $(CD_3)_2CO$) 1.40–2.00 (6H, m), 1.90 (3H, s), 3.47 (1H, dd, *J* 7.7 and 3.3), 3.97–4.06 (1H, m), 5.25–5.32 (1H, m), 7.23–7.28 (3H, m), 7.57–7.62 (2H, m); δ_C (67.5 MHz; $(CD_3)_2CO$) 170.12, 135.00, 134.69, 129.81, 123.73, 73.60, 70.80, 55.61, 33.07, 20.83, 19.69 (2×CH_2); *m*/*z* 314 (M^+, 22.1%), 158 (10.7), 147 (100), 104 (64.2), 97 (41.6), 76 (60.5), 50 (23.5), 43 (60.2).

4.3. (Phenylacetyl)oxycyclohex-2-ene 11

3-Bromocyclohexene (7.00 g, 43.47 mmol), phenylacetic acid (4.08 g, 30 mmol) and diazobicyclo[5.4.0]undec-7-ene (4.49 ml, 30 mmol) were reacted in benzene (100 ml) to give a tan liquid, which on flash column chromatography afforded **11**, as a clear colourless liquid (4.88 g, 76%). (Found: C, 77.87; H, 7.51. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%.) ν_{max} (CCl_4)/cm^{-1} 1727 (CO); δ_H (270 MHz; $CDCl_3$) 1.53–2.15 (6H, m, $CH_2CH_2CH_2$), 3.61 (2H, s, CH_2Ph), 5.24–5.31 (1H, m, OCH), 5.69 (1H, ddt, *J* 10.07, 3.66 and 2.2, OCHCHC*H*), 5.94 (1H, ddt, *J* 10.08, 3.85 and 1.28, OCHC*H*), 7.22–7.35 (5H, m, Ph); δ_C (67.5 MHz; $CDCl_3$) 171.20 (C), 134.21 (C), 132.73 (CH), 129.16 (CH), 128.45 (CH), 126.91 (CH), 124.48 (CH), 68.46 (CH), 41.60 (CH_2), 28.14 (CH_2), 24.78 (CH_2), 18.73 (CH_2); *m*/*z* 216 (M^+, 6%), 136 (3.3), 118 (1.8), 97 (4.1), 91 (42.3), 81 (100).

4.4. (±)-1,2-*trans*-2,3-*cis*-3-(Phenyl)acetyloxy-2-hydroxy-1-phenselanylcyclohexane 12 and (±)-1,2-*trans*-2,3-*cis*-3-(Phenyl)acetyloxy-2-hydroxy-1-phenselanylcyclohexane 13

Phenylacetate **11** (216 mg, 1 mmol), *N*-phenylselanylphthalimide (604 mg, 2 mmol), (±)-camphor-10-sulfonic acid (232 mg, 1 mmol), water (3 drops) and dichloromethane (30 ml) were combined and stirred at room temperature for 12 h. The white precipitate, which had formed was filtered and washed with dichloromethane. The combined filtrate and washings were evaporated in vacuo to give a pale yellow solid. Flash column chromatography (ether/petrol, 1:1) yielded an inseparable mixture of **12** and **13**, as a colourless solid (290 mg, 74%). By analogy with the spectra obtained for **9** and **10**, ^{1}H NMR data were assigned as follows:

Hydroxyselenide **12**: δ_H (270 MHz; $CDCl_3$) 1.30–2.20 (6H, m), 3.16–3.27 (1H, m), 3.47 (1H, dd, *J* 9.9 and 2.8), 3.68 (2H, s), 5.28–5.34 (1H, m), 7.21–7.38 (3H, m), 7.55–7.61 (2H, m); *m*/*z* 390 (M^+, 18.5%), 254 (5.4), 233 (9.6), 157 (7.4), 147 (22.8), 104 (15.3), 91 (100).

Hydroxyselenide **13**: δ_H (270 MHz; $CDCl_3$) 1.30–2.20 (6H, m), 3.05 (1H, dd, *J* 10.1 and 2.9), 3.61 (2H, s), 3.78 (1H, ddd, *J* 10.1, 10.1 and 4.0), 5.42–5.47 (1H, m), 7.21–7.38 (3H, m), 7.55–7.61 (2H, m); *m*/*z* 390 (M^+, 18.5%), 254 (5.4), 233 (9.6), 157 (7.4), 147 (22.8), 104 (15.3), 91 (100).

The mixture was not characterized further, but reacted directly in the next step.

4.5. (±)-*cis*-1-(Phenyl)acetyloxy-2-hydroxycyclohexane 14 and (±)-*trans*-1-(phenyl)acetyloxy-3-hydroxycyclohexane 15

The mixture of selanides **12** and **13** (215 mg, 0.55 mmol), tri-*n*-butyltin hydride (0.3 ml, 1.1 mmol), α,α′-azobisisobutyronitrile (50 mg) and dry benzene (20 ml) was combined and heated to reflux for 12 h. The solution was allowed to cool to room temperature and evaporated in vacuo to give a colourless liquid. Purification by flash column chromatography (ether/petrol, 1:1) yielded **14** as a colourless liquid (49 mg, 38%) and **15**, also as a colourless liquid (46 mg, 36%).

Data for **14**: ν_{max} (CCl_4)/cm^{-1} 3611, 1737; δ_H (270 MHz; $CDCl_3$) 1.22–1.90 (8H, m), 3.66 (2H, s), 3.77–3.85 (1H, m), 4.93 (1H, dt, *J* 7.9 and 2.9), 7.25–7.37 (5H, m); δ_C (67.5 MHz; $CDCl_3$) 171.20, 134.11, 129.11, 128.61, 127.11, 74.49, 69.14, 41.71, 30.16, 26.92, 21.70, 21.14; *m*/*z* 234 (M^+, 0.5%), 136 (2.5), 118 (9.8), 98 (100), 91 (94.6), 81 (78.0).

Data for **15**: (found: 234.1241; $C_{14}H_{18}O_3$ requires 234.1256); ν_{max} (CCl_4)/cm^{-1} 3623, 1735; δ_H (270 MHz; $CDCl_3$) 1.20–1.95 (8H, m), 3.59 (2H, s), 3.86–3.97 (1H, m), 5.10–5.20 (1H, m), 7.22–7.36 (5H, m); δ_C (67.5 MHz; $CDCl_3$) 170.86, 134.18, 129.11, 128.48, 126.97, 70.83, 66.67, 41.76, 38.74, 33.82, 29.81, 19.01; *m*/*z* 234 (M^+, 10.6%), 205 (5.3), 136 (3.4), 118 (4.7), 98 (23.2), 91 (49.0), 81 (100).

4.6. (±)-1,2-*trans*-2,3-*cis*-3-(Phenyl)acetyloxy-2-hydroxy-1-iodocyclohexane 16

Phenylacetate **11** (50 mg, 0.23 mmol), *N*-iodosuccinimide (63 mg, 0.28 mmol), water (2 drops) and dichloromethane (5 ml) were combined and stirred at room temperature for 17 h. The product was absorbed onto silica gel, by adding silica gel and evaporating in vacuo. Flash column chromatography (ether/petrol, 1:1) yielded **16**, as a colourless solid (55 mg, 66%). (Found: C, 46.88; H, 4.84. $C_{14}H_{17}IO_3$

requires C, 46.68; H, 4.76%.) (Found: 342.0091. $C_{14}H_{15}IO_2$ requires 342.0119.) ν_{max} (CCl_4)/cm^{-1} 3569, 1742; δ_H (270 MHz; $CDCl_3$) 1.15–2.35 (7H, m), 3.60 (2H, s), 3.64–3.72 (1H, m), 4.06–4.18 (1H, m), 5.16–5.24 (1H, m), 7.16–7.30 (5H, m); δ_C (67.5 MHz; $CDCl_3$) 170.96, 133.92, 129.16, 128.59, 127.18, 75.48, 71.98, 41.59, 36.63, 34.00, 28.28; *m/z* 360 (M^+, 0.5%), 342 (2.0), 233 (21.4), 137 (20.0), 97 (76.9), 91 (100).

4.7. (±)-*cis*-1-Acetoxy-2-hydroxycyclohexane 17

Selanide **9** (100 mg, 0.32 mmol), tri-*n*-butyltin hydride (0.17 ml, 0.64 mmol), α,α′-azobisisobutyronitrile (50 mg) and dry benzene (20 ml) were combined and heated to reflux for 15 h. The solution was allowed to cool to room temperature and evaporated in vacuo to give a white gel. Purification by flash column chromatography (ether/petrol, 1:1) yielded **17**, as a colourless viscous liquid (38 mg, 75%). ν_{max} (CCl_4)/cm^{-1} 3612, 1737; δ_H (270 MHz; $CDCl_3$) 1.20–1.88 (8H, m), 2.01 (1H, br s), 2.07 (3H, s), 3.82–3.90 (1H, m), 4.89 (1H, dt, *J* 8.3 and 3.0) (upon irradiation at δ 3.86, signal became dd, *J* 8.3 and 3.0); δ_C (67.5 MHz; $CDCl_3$) 170.77, 74.17, 69.05, 30.25, 26.79, 22.00, 21.27, 20.89; *m/z* 116 (3.9%), 115 (3.9), 98 (98.3), 97 (32.6), 79 (32.3), 70 (52.3), 58 (35.0), 43 (100).

4.8. (±)-*trans*-(*tert*-Butyldimethylsilyl)oxy-3-hydroxycyclohexane 18

(1) The selanide **10** (110 mg, 0.35 mmol), tri-*n*-butyltin hydride (0.19 ml, 0.70 mmol), α,α′-azobisisobutyronitrile (50 mg) and dry benzene (20 ml) were combined and heated to reflux for 15 h. The solution was allowed to cool to room temperature and evaporated in vacuo to give a white gel. Purification by flash column chromatography (ether/petrol, 1:1) yielded (±)-*trans*-1-acetoxy-3-hydroxycyclohexane, as a colourless viscous liquid (42 mg, 77%). ν_{max} (CCl_4)/cm^{-1} 3622 and 3473, 1739; δ_H (270 MHz; $CDCl_3$) 1.32–1.94 (8H, m), 2.01 (3H, s), 3.95–4.07 (1H, m), 5.07–5.17 (1H, m); δ_C (67.5 MHz; $CDCl_3$) 170.53, 70.32, 66.75, 38.79, 33.71, 30.03, 21.33, 19.05; *m/z* 140 (1.6%), 115 (2.9), 104 (1.7), 98 (77.5), 80 (34.5), 70 (39.8), 54 (27.9), 43 (100).

(2) (±)-*trans*-1-Acetoxy-3-hydroxycyclohexane (80 mg, 0.51 mmol) and 2,6-lutidine (90 μl, 0.76 mmol) were combined in dry dichloromethane (16 ml) and cooled on an ice bath. (*tert*-Butyldimethylsilyl)methanesulfonate (0.23 ml, 1.01 mmol) was added and stirring was continued for 5 h at room temperature. The reaction mixture was washed with 5% hydrochloric acid (1×5 ml), saturated aqueous sodium hydrogen carbonate (1×5 ml), dried ($MgSO_4$) and evaporated in vacuo to give a colourless liquid.

(3) The crude product from above (110 mg, 0.40 mmol), lithium hydroxide monohydrate (19 mg, 0.44 mmol), water (3 ml) and tetrahydrofuran (24 ml) were combined and refluxed for 15 h. The solution was allowed to cool to room temperature and evaporated in vacuo to give a colourless liquid. Purification by flash column chromatography yielded (±)-**18**, as a colourless liquid (93 mg, 82%). ν_{max} (CCl_4)/cm^{-1} 3623; δ_H (500 MHz; $CDCl_3$) 0.02 (3H, s), 0.03 (3H, s), 0.87 (9H, s), 1.26–1.82 (8H, m), 4.01–4.06 (1H, m), 4.07–4.11 (1H, m); δ_C (125 MHz; $CDCl_3$) 67.62, 67.12, 42.85, 34.63, 33.72, 25.81, 18.92, 18.06, –4.83, −4.86; *m/z* 230 (M^+, 1.2%), 213 (2.4), 173 (31.1), 171 (43.7), 97 (100), 81 (45.3), 75 (51.4).

4.9. [*N*-Cbz-(*R*)-Phenylglycinoyl]oxycyclohex-2-ene 19

3-Bromocyclohexene (3.55 g, 22 mmol), (*R*)-*N*-Cbz-phenylglycine (5.65 g, 19.8 mmol) and diazobicyclo[5.4.0]undec-7-ene (2.96 ml, 19.8 mmol) were reacted in refluxing benzene (100 ml) to give a tan liquid, which on flash column chromatography afforded **19**, as a colourless solid (4.77 g, 67%), as a mixture of diastereoisomers; mp 73–77 °C. (Found: C, 72.15; H, 6.51; N, 3.82. $C_{22}H_{23}NO_4$ requires C, 72.31; H, 6.34; N, 3.83%.) ν_{max} (CCl_4)/cm^{-1} 3436, 1729; δ_H (270 MHz; $CDCl_3$) 1.44–2.12 (6H, m), 5.02–5.17 (2H, m), 5.20–5.32 (1H, m), 5.32–5.39 (1H, m, OCH), 5.41–5.76 (1H, m), 5.82–6.00 (1H, m), 7.25–7.40 (10H, m); δ_C (67.5 MHz; $CDCl_3$) 170.35, 155.31, 155.28, 136.90, 136.78, 136.12, 133.53, 133.23, 128.78, 128.50, 128.37, 128.15, 126.98, 124.72, 124.59, 69.96, 69.65, 67.04, 58.03, 28.06, 27.71, 24.69, 18.67, 18.30; *m/z* 240 (4.8%), 196 (24.9), 91 (100).

4.10. 1,2-*cis*-2,6-*trans*-2-[*N*-Cbz-(*R*)-Phenylglycinoyl]-oxy-6-hydroxy-1-phenselanylcyclohexanes 20 and 21

N-Phenylselanylphthalimide (2.71 g, 8.95 mmol) and **19** (2.81 g, 5.97 mmol) were combined in dry dichloromethane (150 ml).[6] (±)-Camphor-10-sulfonic acid (1.39 g, 5.97 mmol) was added to the mixture, which was stirred at room temperature for 16 h. The white precipitate of phthalimide was filtered, washed with dichloromethane (2×20 ml) and combined filtrate and washings were evaporated in vacuo to give an orange solid. Purification by flash column chromatography (ether/petrol, 1:1) yielded **20** and **21**, as a white gum (2.87 g, 89%). (Found: C, 62.72; H, 5.62; N, 2.95. $C_{28}H_{29}NO_5Se$ requires C, 62.45; H, 5.43; N, 2.60%.) ν_{max} (CCl_4)/cm^{-1} 3437, 1732; δ_H (270 MHz; $CDCl_3$) 1.17–1.80 (6H, m), 1.96 (0.5H, br s of one diastereoisomer), 2.16 (0.5H, br s of other diastereoisomer), 2.90–3.01 (1H, m), 3.60–3.76 (1H, m), 5.03–5.24 (3H, m), 5.36–5.42 (1H, m), 5.88–5.95 (1H, m), 7.27–7.89 (15H, m); *m/z* 539 (M^+, 3.8%), 431 (1.9), 240 (23.7), 196 (22.1), 147 (65.9), 91 (100).

4.11. (1*R*,1′*S*,3*S*)-(−)-3-Hydroxy-1-[*N*-Cbz-(*R*)-phenylglycinoyl]oxycyclohexane 22 and (1*R*,1′*R*,3′*R*)-(−)-3-hydroxy-1-[*N*-Cbz-(*R*)-phenylglycinoyl]oxycyclohexane 23

A mixture of **20** and **21** (1.27 g, 2.37 mmol), tri-*n*-butyltin hydride (1.27 ml, 4.74 mmol), α,α′-azobisisobutyronitrile (50 mg) and dry benzene (30 ml) was combined and heated to reflux for 16 h.[7] The solution was allowed to cool to room temperature and evaporated in vacuo, to give a white gel. Purification by flash column chromatography eluting with ether/petrol (3:1) yielded **22** as a colourless solid (382 mg, 42%) and **23** also as a colourless solid (400 mg, 44%).

Data for **23**: mp 79 °C. (Found: C, 68.89; H, 6.91; N, 3.52. $C_{22}H_{25}NO_5$ requires C, 68.91; H, 6.57; N, 3.65%.) $[\alpha]_D^{24}$ −31.96; ν_{max} (CCl_4)/cm^{-1} 3621, 3435, 1728; δ_H (270 MHz; $(CD_3)_2CO$) 1.21–1.95 (8H, m), 3.85–3.96 (1H, m), 5.06–5.17 (3H, m), 5.31–5.37 (1H, m), 7.14 (1H, d, *J* 7.7), 7.27–7.49 (10H, m); δ_C (67.5 MHz; $(CD_3)_2CO$)

170.73, 156.57, 138.03, 129.41, 129.12, 128.98, 128.60, 128.30, 72.63, 66.87, 66.29, 59.33, 39.47, 34.47, 31.17, 18.93; *m/z* 383 (M^+, 0.6%), 240 (48.6), 196 (33.6), 91 (100).

Data for **22**: mp 120 °C. (Found: C, 68.91; H, 6.66; N, 3.69. $C_{22}H_{25}NO_5$ requires C, 68.91; H, 6.57; N, 3.65%.) $[\alpha]_D^{24}$ −24.02; ν_{max} (CCl_4)/cm^{-1} 3621, 3435, 1729; δ_H (270 MHz; $CDCl_3$) 1.10–1.95 (8H, m), 3.65–3.76 (1H, m), 5.03–5.16 (3H, m), 5.34 (1H, d, *J* 7.8), 7.14 (1H, d, *J* 7.8), 7.29–7.48 (10H, m); δ_C (67.5 MHz; $(CD_3)_2CO$) 170.74, 156.6, 138.01, 129.46, 129.17, 129.01, 128.66, 128.31, 72.64, 66.90, 66.12, 59.41, 39.18, 34.45, 30.86, 19.78; *m/z* 383 (M^+, 0.3%), 240 (24.0), 196 (19.8), 91 (100).

4.12. (1*R*,3*R*)-(−)-1-(*tert*-Butyldimethylsilyl)oxy-3-hydroxycyclohexane (−)-18

(1) Hydroxyester **23** (310 mg, 0.81 mmol) and 2,6-lutidine (0.14 ml, 1.21 mmol) were combined in dry dichloromethane (30 ml) and cooled on an ice bath. *tert*-Butyldimethylsilylmethanesulfonate (0.37 ml, 1.62 mmol) was added and stirring was continued for 15 h at room temperature. The reaction mixture was washed with 5% hydrochloric acid (1×10 ml) and saturated aqueous sodium hydrogen carbonate (1×10 ml), dried ($MgSO_4$) and evaporated in vacuo to give a colourless viscous liquid. Purification by flash column chromatography eluting with ether/petrol (1:4) yielded the silyl ether, as a colourless viscous liquid (338 mg, 84%). (Found: C, 67.94; H, 7.80; N, 3.11. $C_{28}H_{39}NO_5Si$ requires C, 67.57; H, 7.90; N, 2.81%.) $[\alpha]_D^{22}$ −29.34; ν_{max} (CCl_4)/cm^{-1} 3434, 1728; δ_H (270 MHz; $(CD_3)_2CO$) 0.05 (3H, s), −0.04 (3H, s), 0.84 (9H, s), 1.20–1.75 (8H, m), 3.77–3.89 (1H, m), 5.08 (2H, s), 5.05–5.16 (1H, m), 5.34 (1H, d, *J* 7.7), 7.12 (1H, d, *J* 7.7), 7.32–7.49 (10H, m); δ_C (67.5 MHz; $(CD_3)_2CO$) 170.66, 156.54, 138.12, 137.96, 129.49, 129.14, 129.01, 128.63, 128.27, 72.61, 67.96, 66.88, 59.28, 39.63, 34.80, 30.80, 26.12, 19.74, 18.45, −4.71; *m/z* 440 (M^+−57, 5.0%), 342 (29.8), 240 (14.6), 234 (14.5), 196 (10.7), 91 (100).

(2) The ester from step 1 (307 mg, 0.62 mmol), lithium hydroxide monohydrate (26 mg, 0.62 mmol), water (3 ml) and tetrahydrofuran (24 ml) were combined and refluxed for 12 h. Upon cooling to room temperature Merck Kieselgel 60 (0.5 g) was added and the mixture was evaporated to dryness in vacuo. Flash column chromatography eluting with ether/petrol (3:7) yielded (−)-**18**, as a colourless viscous liquid (120 mg, 84%). (Found: 230.1727. $C_{12}H_{26}O_2Si$ requires 230.1702); $[\alpha]_D^{24}$ −4.55 (*c* 1, EtOAc); other data as above, for (±)-**18**.

4.13. (1*S*,3*S*)-(+)-1-(*tert*-Butyldimethylsilyl)oxy-3-hydroxycyclohexane (+)-18

(1) Hydroxyester **22** (246 mg, 0.64 mmol), 2,6-lutidine (0.11 ml, 0.96 mmol) and (*tert*-butyldimethylsilyl)methanesulfonate (0.29 ml, 1.28 mmol) were reacted in dry dichloromethane (30 ml) with stirring for 15 h at room temperature. The reaction mixture was washed with 5% hydrochloric acid (1×10 ml) and saturated aqueous sodium hydrogen carbonate (1×10 ml), dried ($MgSO_4$) and evaporated in vacuo, to give a colourless viscous liquid. Purification by flash column chromatography, eluting with ether/petrol (1:4), yielded the silyl ether, as a colourless viscous liquid (272 mg, 85%). (Found: C, 67.32; H, 7.64; N, 2.54. $C_{28}H_{39}NO_5Si$ requires C, 67.57; H, 7.90; N, 2.81%.) $[\alpha]_D^{22}$ −18.01; ν_{max} (CCl_4)/cm^{-1} 3434, 1727; δ_H (270 MHz; $(CD_3)_2CO$) 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.25–1.85 (8H, m), 3.99–4.10 (1H, m), 5.08 (2H, 2×d, *J* 3.8), 5.06–5.15 (1H, m), 5.34 (1H, d, *J* 7.7), 7.10 (1H, d, *J* 7.7), 7.30–7.50 (10H, m); δ_C (67.5 MHz; $(CD_3)_2CO$) 170.62, 156.51, 138.09, 137.89, 129.39, 129.09, 128.95, 128.60, 128.25, 72.55, 68.09, 66.87, 59.34, 39.86, 34.59, 30.47, 26.15, 19.43, 18.50, −4.66; *m/z* 440 (M^+−^{t}Bu, 5.9%), 342 (26.9), 234 (37.0), 91 (100), 81 (55.2).

(2) The ester from step 1 (230 mg, 0.46 mmol), lithium hydroxide monohydrate (20 mg, 0.46 mmol), water (3 ml) and tetrahydrofuran (24 ml) were combined and refluxed for 12 h. Upon cooling to room temperature Merck Kieselgel 60 (0.5 g) was added and the mixture was evaporated to dryness in vacuo. Flash column chromatography, eluting with ether/petrol (3:7), yielded (+)-**18**, as a colourless viscous liquid (92 mg, 87%). (Found: 230.1722. $C_{12}H_{26}O_2Si$ requires 230.1702.) $[\alpha]_D^{24}$ +4.85 (*c* 1, EtOAc); other data as above, for (±)-**18**.

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References and notes

1. Knight, J.; Sweeney, J. B. *Tetrahedron Lett.* **1998**, *39*, 8703.
2. Bange, J.; Haughan, A. F.; Knight, J. R.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1039; For a review on other syntheses of conduritols and other cyclitols, see: Gultekin, M. S.; Celik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *8*, 1159; For recent syntheses, see: Cere, V.; Minzoni, M.; Pollicino, S.; Ricci, A.; Gasparrini, F.; Ciogli, A.; D'Acquarica, I. *J. Comb. Chem.* **2006**, *8*, 74; Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2005**, *70*, 7829; Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. J. *Eur. J. Org. Chem.* **2005**, 3116; Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H. J. *Eur. J. Org. Chem.* **2005**, 3101; Orsini, F.; Sello, G.; Bernasconi, S.; Fallacara, G. *Tetrahedron Lett.* **2004**, *45*, 9253; Saito, S.; Shimazawa, R.; Shirai, R. *Chem. Pharm. Bull.* **2004**, *52*, 727; Freeman, S.; Hudlicky, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1209 and references cited therein.
3. Haughan, A. F.; Knight, J. R.; Sweeney, J. B. *Tetrahedron Lett.* **1994**, *35*, 1781.
4. Haughan, A. F.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1994**, *5*, 177.
5. Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258.
6. Cooper, M. A.; Ward, A. D. *Tetrahedron* **2004**, *60*, 7963.
7. Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.
8. Nicolaou, K. C. *Tetrahedron* **1981**, *37*, 4097.
9. Anchisi, C.; Maccioni, A.; Maccioni, A. M.; Podda, G. *Gazz. Chim. Ital.* **1983**, *113*, 73; Pedersen, C. *Tetrahedron Lett.* **1967**, 511.

10. Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.
11. For recent discussion on reactions controlled by the Curtin–Hammett principle, see: Wu, H.; Loeppky, R. N.; Glaser, R. *J. Org. Chem.* **2005**, *70*, 6790; Yoon, U. C.; Kwon, H. C.; Hyung, T. G.; Choi, K. H.; Oh, S. W.; Yang, S. R.; Zhao, Z. M.; Mariano, P. S. *J. Am. Chem. Soc.* **2004**, *126*, 1110; Adam, W.; Librera, C.; Trofimov, A. V. *J. Am. Chem. Soc.* **2004**, *125*, 5741; Adam, W.; Librera, C.; Trofimov, A. V. *J. Am. Chem. Soc.* **2002**, *124*, 11936; Howell, S. J.; Ashton, P. R.; Spencer, N.; Philp, D. *Org. Lett.* **2001**, *3*, 353; Chandrasekhar, S. *Res. Chem. Intermed.* **1998**, *24*, 625; Cavalier, J. F.; Fotiadu, F.; Verger, R.; Buono, G. *Synlett* **1998**, 73; Chandrasekhar, S. *Res. Chem. Intermed.* **1997**, *23*, 55; Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351; Pearson, A. J.; Neagu, I. B.; Pinkerton, A. A.; Kirschbaum, K.; Hardie, M. J. *Organometallics* **1997**, *16*, 4346.
12. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1988.