Highly Enantioselective α-Alkenylation of Aldehydes and Ketones

Dieter Enders,* Darren L. Whitehouse

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, D-52074 Aachen, Germany

Fax +49(241)8888127; E-mail Enders@RWTH-Aachen.de

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The enantioselective synthesis of α-substituted β,γ-unsaturated aldehydes and ketones **6** via aldol reaction of SAMP-hydrazones (*S*)-**2** with racemic α-phenylselenyl aldehydes **3** in good overall yields and high enantiomeric excesses (ee = 89–94%) is described.

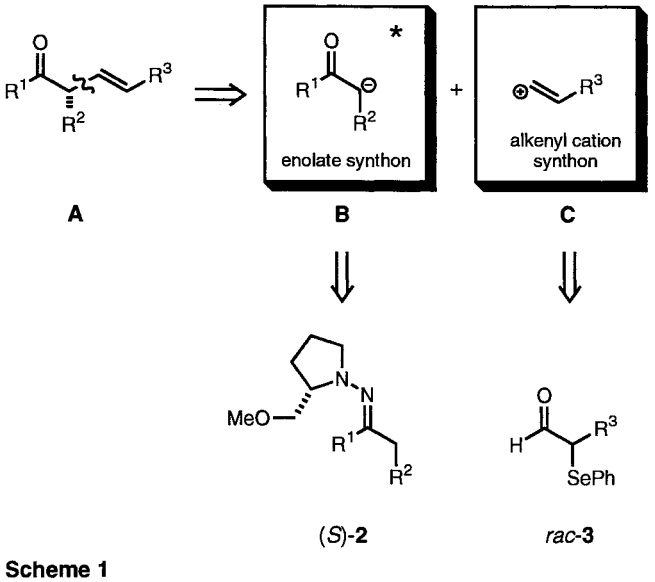
Chiral α-substituted β,γ-unsaturated aldehyde or ketone subunits are found in a very broad range of bioactive compounds and natural products, e.g. in vitamin E side chain,[1] pseudomonic acid,[2] stigmastatriene[3] and levuglandin.[4] Therefore the synthesis of this β,γ-unsaturated carbonyl unit has received considerable attention. These compounds have been synthesised via the α-alkenylation of enolates with either vinyl halides,[5] vinyl and alkynyl sulfones,[6] α-phenylselenylaceto- and α-silyl aldehydes,[7] alkynyl- and alkenyl metal complexes,[8] or via Weinreb's Diels–Alder reaction of chiral *N*-sulfinyl dienophiles,[9] Tadashi's titanium mediated ring contraction,[10] Mutterer's sigmatropic cleavage of unsaturated acetals,[11] titanium(IV) promoted addition of allylic silanes to chiral cyclic anhydrides[12] or via the diastereoselective [2,3]-Wittig rearrangement of tertiary bisallylic ethers.[13] Recently, Yamaguchi et al. have reported the α-alkenylation of ketones via the addition of 1-stannyl alkynes to α-stannyl ketones, although mixtures of α-enones and β-terminal enones were obtained.[14]

However, most of these syntheses suffer from isomerisation of the β,γ-unsaturated carbonyl compounds to the thermodynamically more stable α,β-derivatives when acidic α-protons are present in the molecule.

More interestingly, optically active α-substituted β,γ-unsaturated carbonyl compounds, have been synthesised. Tsuchihashi et al. have reported the triethylaluminium promoted "pinacol-type" rearrangement of enantiopure homoallylic mesylates.[15] The enantioselective photodeconjugation of prochiral α,β-unsaturated ketones, in the presence of catalytic amounts of chiral amino alcohols, leads to α-substituted β,γ-unsaturated ketones with poor to moderate enantiomeric purities (ee = 1–52%) and undefined double bond geometries, whereas the asymmetric photodeconjugation of diacetone D-glucose derived enoates gave excellent diastereoselectivities.[16] Bartik et al. have described the synthesis of 3-methylhex-4-en-2-one via formylation/methylation of nickel-π-allyl complexes. The use of chiral phosphine ligands bound to the metal allows the asymmetric synthesis of this ketone, albeit in modest enantioselectivity (ee = 4–33%).[17]

Herein we wish to report a practical and versatile synthesis of chiral α-substituted β,γ-unsaturated aldehydes and ketones with both high enantio- and regiocontrol employing our well established SAMP-hydrazone aldol reaction of both aldehyde and ketone SAMP-hydrazones (*S*)-**2** with racemic α-phenylselenyl aldehydes *rac*-**3**.

Retrosynthetic analysis of the chiral α-substituted β,γ-unsaturated carbonyl compounds **A** by heterolytic cleavage of the C-α/C-β bond leads to the enolate synthon **B** and the alkenyl cation synthon **C**. Enolate **B** can be seen to come from the SAMP-hydrazones (*S*)-**2**. The α-phenylselenyl aldehydes *rac*-**3** are synthetic equivalents of the alkenyl cation **C** via aldol reaction with hydrazone (*S*)-**2** and subsequent non-oxidative elmination of both hydroxyl and phenylselenyl moieties.



Scheme 1

Aldol reaction of the racemic α-phenylselenyl aldehydes **3**, prepared using the method described by Sonoda,[18] with the azaenolate of the known SAMP-hydrazone **2**[19] (*t*-BuLi, THF, −100 °C for ketone hydrazones **2**; LDA, THF, 0 °C then −100 °C for propanal hydrazone **2**) afforded a diastereomeric mixture of γ-phenylselenyl-β-hydroxyhydrazones **4a–i** in good yield (76–88%) and very high asymmetric induction with respect to the SAMP-hydrazone α-stereogenic centre. The absolute configuration given for the new stereocentre is based on the relative topicity detected for electrophilic substitutions of SAMP/RAMP-hydrazones.[20] The lithium azaenolate is attacked by the corresponding aldehyde *syn* to the intramolecularly coordinated lithium, located below the C-1,C-2,N,N plane of the azaenolate, in a "metalloretentive" mechanism. From previous results of our research group[19] the C-α/C-β centres were assigned a *syn* and an *anti* relationship by NMR spectroscopy although the C-γ centre was not unambiguously assigned since subsequent double bond formation would remove both C-β/C-γ-centres.

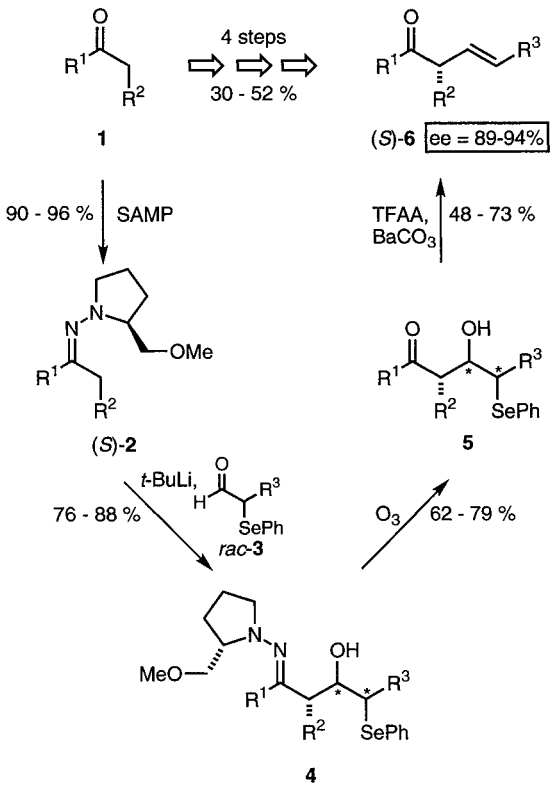
Oxidative cleavage of the hydrazone unit with reductive workup was carried out according to the literature procedure,[21] with no observable oxidative elimination of

selenium, to afford the carbonyl compounds **5a–i** (62–79%). No epimerisation of the α-centre was observed in the oxidative cleavage step as shown by $^1H/^{13}C$ NMR spectroscopy (de = 91–96%). The α-stereogenic centre was assigned the (*S*)-configuration based on the accepted mechanism of SAMP-aldol reactions and on previous extension of this method to the enantio- and diastereoselective synthesis of L-*threo*- and D-*erythro*-sphingosine.[22]

Elimination of the hydroxyl and phenylselenyl moieties was carried out under modified Krief conditions[23] using trifluoroacetic anhydride–barium carbonate to afford the β,γ-unsaturated carbonyl compounds **6a–g** with complete (*E*)-double bond formation (as observed by $^1H/^{13}C$ NMR) and little or no racemisation of the α-stereogenic centre (0–5%) in moderate to good yield (48–73%). For examples (*S*)-**6h, i** it proved impossible to isolate the β,γ-unsaturated aldehydes, presumably due to the increased volatility of these products. As can be seen in the example of dioxanone **6f** this method is compatible with more highly functionalised carbonyl compounds and an extension of this procedure to natural product chemistry has already been successfully carried out in our laboratories.[22]

The use of more soluble bases to buffer the trifluoroacetic acid formation caused considerable racemisation of the carbonyl compounds (e.g. 10–20% for K_2CO_3, complete racemisation for NEt_3); although, no isomerisation of the double bond into conjugation was observed.

The ee values of carbonyl compounds **6a–g** were determined by $^1H/^{13}C$ NMR spectroscopy of the corresponding "Noyori acetals" **7a–g** (de = 89–94%) prepared under standard literature conditions [(*R,R*)-2,3-butanediol bis(trimethylsilyl) ether, cat. TMSOTf, CH_2Cl_2, 0°C, 88–93%][24] by comparison with the corresponding diastereomeric acetals, prepared after prior racemisation of a sample of the carbonyl compound **6** (NEt_3, CH_2Cl_2, RT, overnight).



4-7	R1	R2	R3
a	Et	Me	Pr
b	Et	Me	*i*-Pr
c	Et	Me	Non
d	-(CH2)4-		Pr
e	-(CH2)4-		Non

4-7	R1	R2	R3
f	-CH2OCMe2O-		Pr
g	H	Me	Non
h	H	Me	Pr
i	H	Me	*i*-Pr

Scheme 2

Epimerisation of the α-centre of the carbonyl compounds was also observed on prolonged standing; hence, it is

Table 1. Preparation of α-Substituted β,γ-Unsaturated Ketones and Aldehydes (*S*)-**6** and Their Corresponding Acetals (*S,R,R*)-**7**[a]

6,7	R1	R2	R3	Yield (%)[b] 5→6	$[\alpha]_D^{r.t.}$ 6	Yield (%)[b,c] 5→7	$[\alpha]_D^{r.t.}$ 7	ee (de) (%)[d] 6,7
a	Et	Me	Pr	78	+175.9	67 (75)	−21.8	92 (94)
b	Et	Me	*i*-Pr	72	+143.9	57 (79)	−9.4	90 (92)
c	Et	Me	Non	81	+114.7	73 (88)	−4.7	94 (94)
d	−(CH2)4−		Pr	76	−17.0	62 (75)	−7.8	89 (92)
e	−(CH2)4−		Non	70	−6.1	52 (80)	−5.4	90 (90)
f	−CH2OC(Me)2O−		Pr	64	−114.2	48 (45)	−10.8	93 (92)
g	H	Me	Non	67	+4.2	52 (82)	−8.3	92 (95)
h	H	Me	Pr	–	–	– (58)	−8.8	– (92)
i	H	Me	*i*-Pr	–	–	– (72)	−195	– (94)

[a] All optical rotations were measured in Uvasol grade $CHCl_3$ at concentrations $c = 1.00 \pm 0.05$ at temperatures T = 26°C ± 1°C.
[b] Based on isolated material after purification by flash column chromatography.
[c] Yields for the one-step preparation of acetals **7** are given in parentheses (Method B).
[d] ee Values of **6** were measured by ^1H NMR spectroscopy as the de values of the corresponding chiral acetals **7**: de values for the one-step preparation of acetals **7** are given in parentheses.

advisable to store these compounds as their corresponding chemically and optically stable acetals.

Interestingly, the one-pot elimination hydroxyl/selenyl moieties with concomitant carbonyl protection could be performed under modified acetal forming conditions [(*R,R*)-2,3-butanediol bis(trimethylsilyl) ether, 1.0 equiv TMSOTf, CH_2Cl_2, r.t.] to give the acetals **7a–i**, once again with complete (*E*)-double bond geometry and without any observable epimerisation of the α-stereogenic centre (^{1}H NMR; de = 91–95%, yield: 45–88%). The preparation of acetals **7h, i** appears to show the slightly wider applicability, especially to lower molecular weight compounds, of this one-pot method (Method B). Obviously the use of the enantiomeric RAMP would give access to the enantiomeric aldehydes and ketones with (*R*)-configuration at the α-stereogenic centre.

In summary, an efficient and highly enantioselective method for the α-alkenylation of both aldehydes and ketones is described (ee = 89–94%, complete (*E*)-double bond regioselectivity) which compares most favourably, in terms of asymmetric induction, ease of preparation and especially scope of applicability, to previously reported asymmetric α-alkenylation methods.

Solvents were dried and purified prior to use. THF was freshly distilled from K under Ar. CH_2Cl_2 was distilled from CaH_2 and stored under Ar. Et_2O and pentane were distilled prior to use. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured using a Perkin–Elmer P241 polarimeter using solvents of Merck Uvasol quality. Microanalyses were obtained with a CHN-O-RAPID elemental analyser. ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR 300, Gemini 300 (300 and 75 MHz) using TMS as internal standard. IR spectra were recorded on a Beckman Acculab 4 and a Perkin–Elmer FT/IR 1750 spectrophotometer as evaporated films. Mass spectroscopic analyses were obtained on a Varian MAT

Table 2. Spectroscopic Data for α-Substituted β,γ-Unsaturated Carbonyl Compounds (S)-**6**[a]

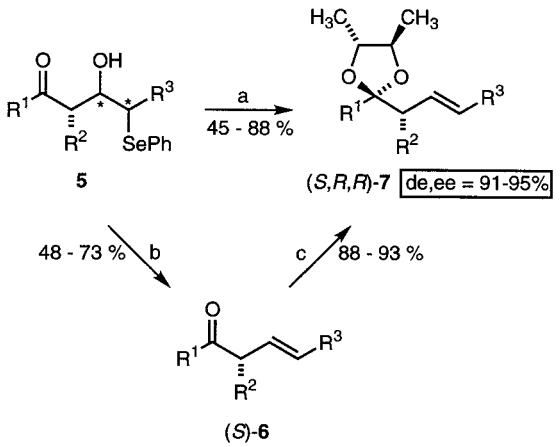
Product	IR (neat) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
6a	2958, 2924, 2868, 2838, 1712, 1458, 1448, 1378, 969, 910, 802, 741	0.88 (t, J = 7.2, 3H, C-9 Me), 1.02 (t, J = 7.1, 3H, C-1 Me), 1.14 (d, J = 6.9, 3H, C-4 Me), 1.46 (m, 2H, 2 × H-8), 1.98 (m, 2H, 2 × H-6), 2.44 (m, 1H, H-2), 2.54 (m, 1H, H-2), 3.16 (dq, J = 6.4, 6.9, 1H, H-4), 5.38 (ddt, J = 1.4, 8.2, 15.1, 1H, H-6), 5.56 (dtd, J = 0.8, 6.4, 15.1, 1H, H-5)	7.86 (C-1), 13.60 (C-9), 16.38 (C-1′), 22.40 (C-8), 33.72 (C-7), 34.62 (C-2), 50.22 (C-4), 129.59 (C-6), 133.02 (C-5), 212.83 (C-3)	154 ($M^{+\cdot}$, 3), 151 (80) 85 ($M^{+\cdot}$ −CHCHPr, 39), 57 ($EtCO^+$, 100)
6b	2958, 2930, 2862, 1709, 1572, 1470, 1434, 1220, 1152, 1022, 964, 732	0.88 (t, J = 7.1, 3H, C-1 Me), 0.97 (d, J = 6.7, 6H, 2 × Me, C-8, C-9), 1.14 (d, J = 6.9, 3H, C-4 Me), 2.26 (m, 1H, H-7), 2.50 (dq, J = 7.1, 14.1, 2H, 2 × H-2), 3.13 (dq, J = 6.5, 6.9, 1H, H-4), 5.33 (ddd, J = 1.4, 8.4, 15.4, 1H, H-6), 5.54 (dd, J = 6.5, 15.4, 1H, H-5)	7.88 (C-1), 16.40 (C-1′), 22.27 (C-8), 22.34 (C-9), 31.08 (C-7), 33.68 (C-2), 50.12 (C-4), 126.49 (C-6), 140.17 (C-5), 212.85 (C-3)	154 ($M^{+\cdot}$, 23), 151 (100), 111 ($M^{+\cdot}$ −*i*-Pr, 9), 57 ($EtCO^{+\cdot}$, 28)
6c	2942, 2918, 2906, 2842, 1708, 1458, 1212, 1160, 962, 728	0.88 (t, J = 6.8, 3H, C-15 Me), 1.03 (t, J = 7.2, 3H, C-1 Me), 1.14 (d, J = 6.8, 3H, C-4 Me), 1.26 (br s, 14H, lipophilic chain), 1.99 (app. q, J = 6.9, 2H, 2 × H-7), 2.50 (dq, J = 7.2, 14.2, 2H, 2 × H-2), 3.15 (dq, J = 6.8, and 7.3, 1H, H-4), 5.35 (ddd, J = 1.0, 7.9, 15.4, 1H, H-6), 5.56 (dt, J = 6.6, 15.4, 1H, H-5)	7.88 (C-1), 14.14 (C-15), 16.37 (C-1′), 22.73 (C-14), 29.16, 29.27, 29.36, 29.51, and 29.62, 31.95 (C-8 to C-13), 32.57 (C-2), 32.72 (C-7), 50.23 (C-4), 129.34 (C-6), 133.31 (C-5), 212.83 (C-3)	238 ($M^{+\cdot}$, 16), 235 (92), 195 ($M^{+\cdot}$ −Pr, 27), 57 ($EtCO^{+\cdot}$, 100)
6d	2952, 2922, 2868, 1707, 1446, 1124, 1068, 962, 930	0.89 (t, J = 7.1, 3H, C-5′ Me), 1.40 (m, 2H, 2 × H-4′), 1.58–2.02 (m, 6H, 2 × H-3, 2 × H-4, 2 × H-5), 2.31–2.46 (m, 2H, 2 × H-6), 2.53 (m, 1H, H-2), 5.44 (dtd, J = 1.0, 6.6, 15.6, 1H, H-2′), 5.61 (ddt, J = 1.1, 5.2, 15.4, 1H, H-1′)	13.63 (C-5′), 22.47 (C-4′), 24.30 (C-4), 27.67 (C-5), 34.52 (C-3), 34.76 (C-3′), 41.60 (C-6), 53.89 (C-2), 127.52 (C-2′), 132.49 (C-1′), 212.08 (C-1)	166 ($M^{+\cdot}$, 41), 165 ($M^{+\cdot}$ −H, 61), 137 ($M^{+\cdot}$ −Et, 33), 123 ($M^{+\cdot}$ −Pr, 30)
6e	2972, 2958, 2862, 2844, 1712, 1452, 1382, 1246, 1100, 968, 932, 836	0.88 (t, J = 6.9, 3H, C-11′ Me), 1.26 (br s, 14H, lipophilic chain), 1.62–2.06 (m, 6H, 2 × H-3, 2 × H-4, 2 × H-5), 2.20–2.26 (m, 1H, H-2), 5.44 (tdd, J = 1.1, 6.6, 15.6, 1H, H-2′), 5.61 (ddt, J = 1.0, 7.1, 15.6, 1H, H-1′)	14.13 (C11′), 22.22 (C-10′), 26.44 (C-4), 27.67, 29.17, 29.23, 29.34, 29.50, 29.56, 31.92, 32.69 (C-4′ to C-9′, C-3, C-5), 38.10 (C-3′), 41.59 (C-6), 53.87 (C-2), 129.11 (C-2′), 131.09 (C-1′), 210.03 (C-1)	250 ($M^{+\cdot}$, 85), 249 ($M^{+\cdot}$ −H, 70), 221 ($M^{+\cdot}$ −Et, 12), 207 ($M^{+\cdot}$ −Pr, 16)
6f	2982, 2958, 2922, 2878, 1746, 1452, 1372, 1220, 1152, 964, 874	0.90 (t, J = 6.9, 3H, C-5′ Me), 1.35–1.58 [m, 8H, including 1.43 and 1.48 (both s, 3H, 2 × acetonide-Me) and 2 × H-4′], 2.06 (app. q, J = 7.4, 2H, 2 × H-3′), 4.01 (d, J = 16.7, 1H, H-6), 4.29 (dd, J = 1.0, 16.7, 1H, H-6), 4.66 (dd, J = 1.0, 6.4, 1H, H-2), 5.49 (ddt, J = 1.0, 6.4, 15.6, 1H, H-2′), 5.82 (tdd, J = 1.0, 6.5, 15.6, 1H, H-1′)	13.71 (C-5′), 21.95 (C-4′), 23.73, 24.15 (2 × C-2 Me), 34.56 (C-3′), 66.68 (C-6), 75.93 (C-4), 100.87 (C-2), 121.91 (C-2′), 137.43 (C-1′), 207.86 (C-5)	198 ($M^{+\cdot}$, 14), 155 ($M^{+\cdot}$ −Pr, 16), 134 [$M^{+\cdot}$ −$(CH_3)_2CO$, 100]
6g	2972, 2906, 2840, 2746, 1718, 1430, 1248, 1072, 970, 838	0.88 (t, J = 6.9, 3H, C-13 Me), 1.26 (br s, 14H, lipophilic chain), 1.38 (d, J = 7.2, 3H, C-2 Me), 2.04 (m, 2H, × H-5), 2.38 (m, 1H, H-2), 5.36 (ddt, J = 1.3, 6.0, 15.4, 1H, H-4), 5.80 (dtd, J = 1.4, 6.9, 15.4, 1H, H-3), 9.40 (d, J = 1.7, 1H, H-1)	13.68 (C-13), 14.12 (C-1′), 22.70 (C-12), 28.10, 28.40, 29.12, 29.34, 29.48, 29.55 (C-6 to C-11), 31.90 (C-5), 32.76 (C-2), 129.20 (C-3), 131.66 (C-4), 205.96 (C-1)	210 ($M^{+\cdot}$, 1), 181 ($M^{+\cdot}$ −Et, $M^{+\cdot}$ −CHO, 10)

[a] Satisfactory microanalyses and/or HRMS obtained for **6a–g**: C, H: 0.4 and/or ± 0.0005 amu.

Table 3. Spectroscopic Data for α-Substituted-β,γ-Unsaturated Acetals (*S,R,R*)-**7**[a,b]

Product	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
7a	2960, 2922, 2862, 1464, 1438, 1376, 1092, 998, 972, 946	0.88 (t, J = 7.4, 6H, 2 × Me, C-1, C-9), 1.01 (d, J = 6.9, 3H, C-4 Me), 1.22 (d, J = 4.9, 3H, C-2′ Me), 1.25 (d, J = 4.7, 3H, C-3′ Me), 1.36 (m, 2H, 2 × H-8), 1.62 (m, 2H, 2 × H-2), 1.98 (m, 2H, 2 × H-7), 2.41 (m, 1H, H-4), 3.63 (m, 2H, H-2′, H-3′), 5.48 (m, 2H, H-5, H-6)	7.62 (C-1), 13.67 (C-9), 15.31 (C-4 Me), 16.69, 17.00 (C-2′ Me, C-3′ Me), 22.66 (C-8), 29.29 (C-2), 34.59 (C-7), 44.59 (C-4), 78.94, 79.12 (C-2′, C-3′), 112.52 (C-3), 129.29 (C-6), 131.75 (C-5)	225 ($M^{+\cdot}$ −H, 6), 197 ($M^{+\cdot}$ −Et, 9), 129 ($M^{+\cdot}$ −CHMeCHCHPr, 100)
7b	2960, 2924, 2864, 1460, 1376, 1152, 1094, 1000, 974, 948	0.88 (t, J = 7.4, 3H, C-1 Me), 0.97 (d, J = 6.9, 6H, 2 × Me, C-8, C-9), 1.00 (d, J = 6.9, 3H, C-4 Me), 1.22 (d, J = 4.4, 3H, C-2′ Me), 1.24 (d, J = 4.6, 3H, C-3′ Me), 1.61 (dq, J = 1.3, 7.4, 2H, 2 × H-2), 2.26 (m, 1H, H-7), 2.39 (m, 1H, H-4), 3.64 (m, 2H, H-2′, H-3′), 5.39 (m, 2H, H-5, H-6)	7.63 (C-1), 15.31 (C-4 Me), 16.66, 16.99 (C-2′ Me, C-3′ Me), 22.57 (2 × C, C-8, C-9), 29.-42 (C-7), 31.13 (C-2), 44.46 (C-4), 78.90, 79.14 (C-2′, C-3′), 112.57 (C-3), 128.44 (C-6), 138.23 (C-5)	225 ($M^{+\cdot}$ −H, 2), 197 ($M^{+\cdot}$ − Et, 4), 129 ($M^{+\cdot}$ −CHMeCHCH-*i*Pr, 100)
7c	2962, 2918, 2864, 2846, 1458, 1374, 1090, 1002, 974, 948	0.81 (t, J = 7.4, 6H, 2 × Me, C-1, C-15), 0.93 (d, J = 6.9, 3H, C-4 Me), 1.15 (d, J = 3.6, 3H, C-2′ Me), 1.17 (d, J = 3.9, 3H, C-3′ Me), 1.20 (br s, 14H, lipophilic chain), 1.58 (dq, J = 1.4, 7.4, 2H, 2 × H-2), 1.93 (m, 2H, 2 × H-7), 2.34 (m, 1H, H-4), 3.55 (m, 2H, H-2′, H-3′), 5.37 (m, 2H, H-5, H-6)	7.62 (C-1), 14.14 (C-15), 15.30 (C-4 Me), 16.69, 17.00 (C-2′ Me, C-3′ Me), 22.70 (C-14), 29.19, 29.29 (2 × C), 29.34, 29.53 (C-8–C-12), 29.62 (C-2), 31.93 (C-13), 32.72 (C-7), 44.56 (C-4), 78.93, 79.10 (C-2′, C-3′), 112.52 (C-3), 131.31 (C-6), 131.44 (C-5)	309 ($M^{+\cdot}$ −H, 1), 281 ($M^{+\cdot}$ −Et, 10), 129 ($M^{+\cdot}$ −CHMeCHCH-C_9H_{19}, 100)
7d	2974, 2964, 2860, 2832, 1460, 1384, 1096, 1002, 972, 938	0.89 (t, J = 7.1, 3H, C-5′ Me), 1.18 (d, J = 5.7, 3H, C-2″ Me), 1.23 (d, J = 5.8, C-3″ Me), 1.31–1.78 (m, 10H, 2 × H-3, 2 × H-4, 2 × H-5, 2 × H-6, 2 × H-4′), 1.98 (m, 2H, 2 × H-3′), 2.15 (m, 1H, H-2), 3.57 (m, 2H, H-2″, H-3″), 5.47 (m, 2H, H-1′ H-2′)	13.73 (C-5″), 15.91, 17.54 (C-2″ Me, C-3″ Me), 22.63 (C-4′), 24.02 (C-4), 24.71 (C-5), 30.57 (C-3′), 34.96 (C-3), 36.82 (C-6), 49.68 (C-2), 77.84, 78.61 (C-2″, C-3″), 109.36 (C-1), 129.18 (C-2′), 130.02 (C-1′)	238 ($M^{+\cdot}$, 15), 223 ($M^{+\cdot}$ −Me, 6), 209 ($M^{+\cdot}$ −Et, 13), 195 ($M^{+\cdot}$ −Pr, 11), 127 (100)
7e	2972, 2916, 2842, 1452, 1432, 1378, 1148, 1112, 974, 932	0.88 (t, J = 6.9, 3H, C-11′ Me), 1.16 (d, J = 5.8, 3H, C-2″ Me), 1.23 (d, J = 5.8, C-3″ Me), 1.27 (br s, 14H, lipophilic chain), 1.40–1.82 (m, 8H, 2 × H-3, 2 × H-4, 2 × H-5, 2 × H-6), 2.01 (m, 2H, 2 × H-3′), 2.16 (m, 1H, H-2), 3.56 (m, 2H, H-2″, H-3″), 5.47 (m, 2H, H-1′, H-2′)	14.13 (C-11′), 15.91, 17.22 (C-2″ Me, C-3″ Me), 22.69 (C-10′), 24.03 (C-4), 24.70 (C-5), 29.20, 29.36, 29.49, 29.56 (2 × C, C-4′ to C-8″), 29.64 (C-9′), 30.59 (C-3), 31.92 (C-3′), 32.81 (C-6), 49.70 (C-2), 77.83, 78.59 (C-2″, C-3″), 109.61 (C-1), 129.82 (C-2′), 131.49 (C-1′)	322 ($M^{+\cdot}$, 16), 279 ($M^{+\cdot}$ −Pr, 5), 195 ($M^{+\cdot}$ −C_9H_{19}, 1), 127 (100)
7f	2958, 2922, 2962, 1452, 1436, 1378, 1140, 1112, 972, 732	0.92 (t, J = 6.9, C-5′ Me), 1.18 (d, J = 6.7, 3H, C-2″ Me), 1.27 (d, J = 6.9, 3H, C-3″ Me), 1.26 (br s, 6H, 2 × H-3′), 3.50–3.78 (m, 4H, 2 × H-6, H-2″, H-3″), 4.94 (dd, J = 1.2, 4.2, H-2), 5.26 (dt, J = 7.6, 15.4, 1H, H-2′), 5.49 (dt, J = 6.9, 15.4, 1H, H-1′)	14.28 (C-5′), 22.46, 22.87 (C-2″ Me, C-3″ Me), 23.56, 24.12 (2 × C-2 Me), 27.78 (C-4′), 32.96 (C-3′), 63.82 (C-6), 69.54 (C-4), 77.87, 78.11 (C-2″, C-3″), 101.19 (C-2), 112.03 (C-5), 129.67 (C-2′), 130.93 (C-1′)	270 ($M^{+\cdot}$, 3), 227 ($M^{+\cdot}$ −Pr, 23), 232 [$M^{+\cdot}$ −$(CH_3)_2CO$, 56], 171 [$M^{+\cdot}$ −$(CH_3)_2CO$-Pr, 51]
7g	2946, 2916, 2842, 1452, 1376, 1152, 1082, 962	0.88 (t, J = 6.9, 3H, C-13 Me), 1.02 (d, J = 6.8, 3H, C-2 Me), 1.22 (d, J = 5.8, 3H, C-2′ Me), 1.26 (br s, 14H, lipophilic chain), 1.37 (d, J = 6.6, 3H, C-3′ Me), 2.03 (m, 2H, 2 × H-5), 2.35 (m, 1H, H-2), 3.58 (m, 2H, H-3, H-4)	14.13 (C-13), 16.72, 17.19 (C-2′ Me, C-3′ Me), 19.12 (C-2 Me), 22.70 (C-12), 29.19, 29.31, 29.48, 29.55, 29.67 (C-6 to C-10), 31.96 (C-11), 32.09 (C-5), 41.19 (C-2), 78.39, 79.57 (C-2′, C-3′), 106.09 (C-1), 130.11 (C-4), 131.74 (C-3)	282 ($M^{+\cdot}$, 3), 267 ($M^{+\cdot}$ −Me, 34), 253 ($M^{+\cdot}$ −CHO, $M^{+\cdot}$ −Et, 58), 101 ($M^{+\cdot}$ −CHMeCHCH-C_9H_{19}, 100)
7h	2958, 2922, 2862, 1452, 1378, 1110, 1088, 968	0.89 (t, J = 7.2, 3H, C-7 Me), 1.03 (d, J = 6.8, 3H, C-2 Me), 1.22 (d, J = 5.8, C-2′ Me), 1.29 (d, J = 5.9, 3H, C-3′ Me), 1.38–1.42 (m, 2H, 2 × H-6), 2.00 (dq, J = 1.0, 6.8, 2H, 2 × H-5), 2.34 (m, 1H, H-2), 3.58 (m, 2H, H-2′, H-3′), 4.89 (d, J = 4.1, 1H, H-1), 5.44 (ddd, J = 4.1, 6.9, 15.4, 1H, H-4), 5.51 (dd, J = 6.1, 15.4, 1H, H-3)	13.65 (C-7), 14.42 (C-2 Me), 16.72, 17.19 (C-2′ Me, C-3′ Me), 22.58 (C-6), 34.82 (C-5), 41.16 (C-2), 78.87, 79.57 (C-2′, C-3′), 106.09 J = (C-1), 130.37 (C-4), 131.45 (C-3)	198 ($M^{+\cdot}$, 2), 197 ($M^{+\cdot}$ −H, 35), 169 ($M^{+\cdot}$ −Et, 21), 155 ($M^{+\cdot}$ −Pr, 25), 101 ($M^{+\cdot}$ −CHMeCHCHPr, 100)
7i	2956, 2922, 2864, 1456, 1250, 1112, 972, 842	0.98 (d, J = 6.9, 6H, 2 × Me, C-6, C-7), 1.02 (d, J = 6.8, 3H, C-2 Me), 1.22 (d, J = 5.4, 3H, C-2′ Me), 1.27 (d, J = 5.8, 3H, C-3′ Me), 2.25 (m, 1H, H-5), 2.34 (m, 1H, H-2), 3.58 (m, 2H, H-2′, H-3′), 4.91 (d, J = 4.1, 1H, H-1), 5.36 (ddd, J = 1.0, 5.1, 15.6, 1H, H-4), 5.48 (dd, J = 6.0, 15.6, 1H, H-3)	14.38 (C-2 Me), 16.69, 17.16 (C-2′ Me, C-3′ Me), 22.60, 22.84 (C-6, C-7), 31.08 (C-5), 41.09 (C-4), 78.41, 79.52 (C-2′, C-3′), 106.18 (C-1), 129.41 (C-3), 133.91 (C-2)	198 ($M^{+\cdot}$, 5), 197 ($M^{+\cdot}$ − H, 15), 169 ($M^{+\cdot}$ −Et, 20), 155 ($M^{+\cdot}$ −*i*-Pr, 37), 101 ($M^{+\cdot}$ − CHMeCHCH-*i*Pr, 100)

[a] Atom numbering for acetals **7a–i** is reported as for the corresponding carbonyl compounds (see Table 2) for ease of comparison.
[b] Satisfactory microanalyses and/or HRMS obtained for **7a–i**: C, H ± 0.4 and/or 0.0008 amu.



a) (*R,R*)-butane-2,3-diol *bis*-(trimethylsilyl)-ether, TMSOTf (1.0 eq.), CH_2Cl_2, RT; b) $BaCO_3$, TFAA, CH_2Cl_2; c) (*R,R*)-butane-2,3-diol *bis*-(trimethylsilyl)-ether, cat. TMSOTf, CH_2Cl_2, 0°C

Scheme 3

212, EI 70 eV. High resolution mass spectra were recorded on a Finnigan MAT, MAT 95 spectrometer.

For ketones **1** (diethyl ketone, cyclohexanone and 2,2-dimethyl-[1,3]-dioxan-5-one) the corresponding SAMP hydrazones **2** were prepared according to the literature procedure[19] from the ketone **1** (20.0 mmol) and SAMP (20.0 mmol) in benzene (50 mL) at 80°C with azeotropic water removal (Dean–Stark trap). For propanal SAMP-hydrazone, stirring an equimolar mixture of the propanal (20.0 mmol) and SAMP (20.0 mmol) in anhyd Et_2O (50 mL) at r.t. was sufficient to afford the corresponding hydrazone **2** in excellent yield.[19] The α-phenylselenyl aldehydes **3** were prepared according to the method of Sonoda et al.[18] starting from freshly distilled pentanal, 3-methylbutanal and undecanal.

γ-Phenylselenyl-β-hydroxyhydrazones 4; General Procedure:
Ketone Hydrazones **4a–f**: To a solution of ketone SAMP-hydrazone **2** (5.0 mmol) in anhyd THF (25 mL) at −80°C under an atmosphere of Ar, was added *t*-BuLi (1.6 M solution in pentane) (5.5 mmol). This solution was stirred at −80°C for 30 min and then cooled to −100°C. A precooled (−70°C) solution of aldehyde **3** (6.0 mmol) in THF (10 mL) was added dropwise using a cannula. The resultant solution was stirred for 1 h at −100°C, allowed to warm to −70°C over 2 h and then poured into sat. NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 25 mL). The combined ethereal phase was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel: pentane/Et_2O, 2:1) afforded the aza-aldol products **4a–f** as viscous yellow oils.

Aldehyde Hydrazones **4g–i**: Propanal SAMP-hydrazone **2** (5.0 mmol) in anhyd THF (10 mL) was added dropwise to a solution of LDA (5.25 mmol) in THF (25 mL) at 0°C under an atmosphere of Ar. This solution was stirred at 0°C for 4 h and then cooled to −100°C. The addition of aldehyde **3** (6 mmol), workup and purification was carried out as described above affording the aldol products **4g–i** as viscous pale yellow oils.

β-Hydroxy-γ-phenylselenyl Carbonyl Compounds 5; General Procedure:
Ozone was bubbled through a solution of hydrazone **4** (2.0 mmol) in pentane (30 mL) at −70°C until complete consumption of the starting material was observed (TLC control). Ar was bubbled through the solution to remove any excess ozone, and then Ph_3P (6.0 mmol) was added in one portion. The resultant suspension was stirred at −70°C for 4 h and allowed to warm to r.t. overnight. Filtration through Celite and concentration in vacuo afforded the crude products, which were purified by flash column chromatography (silica gel: pentane/Et_2O, 4:1) affording the carbonyl compounds **5** as colourless oils.

β,γ-Unsaturated Carbonyl Compounds 6 and Their Corresponding Acetal Protected Derivatives 7; General Procedure:
Method A (*via β,γ-Unsaturated Carbonyl Compounds* **6**): $BaCO_3$ (1.97 g, 10.0 mmol) was added to a solution of **5** (1.0 mmol) in anhyd CH_2Cl_2 (30 mL) at −20°C under an atmosphere of Ar followed by dropwise addition of trifluoroacetic anhydride (TFAA, 1.05 g, 5.0 mmol). The suspension was allowed to warm immediately to r.t. and then stirred for 24–48 h (TLC control). The mixture was filtered through Celite (plus pentane washings) and then poured into water and extracted with pentane (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to give the crude carbonyl compounds **6**. These could be quickly purified by rapid filtration through silica gel (pentane then pentane/Et_2O, 10:1). Alternatively the crude reaction mixture was redissolved in anhyd CH_2Cl_2 (10 mL) at 0°C under an atmosphere of Ar. (*R,R*)-2,3-Butanediol bis(trimethylsilyl) ether (468 mg, 2.0 mmol) was added, followed by the addition of a catalytic amount of TMSOTf (1 drop). This mixture was stirred for 2 h at 0°C, poured into water, extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (silica gel: pentane, then pentane/Et_2O, 10:1) afforded the acetals **7** as colourless oils.

Method B (*Direct Acetal Formation*): To a solution of **5** (0.5 mmol) in anhyd CH_2Cl_2 at r.t. under an atmosphere of Ar was added (*R,R*)-2,3-butanediol bis(trimethylsilyl)ether (234 mg, 1.0 mmol) and then TMSOTf (222 mg, 1.0 mmol). The solution was stirred at r.t. overnight, poured into water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (silica gel: pentane, then pentane/Et_2O 20:1) afforded the (*R,R*)-acetals **7** as colourless oils.

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