Asymmetric Synthesis of α'-Silylated α-Iodo Ketones *via* Iodination with Trifluoroiodomethane

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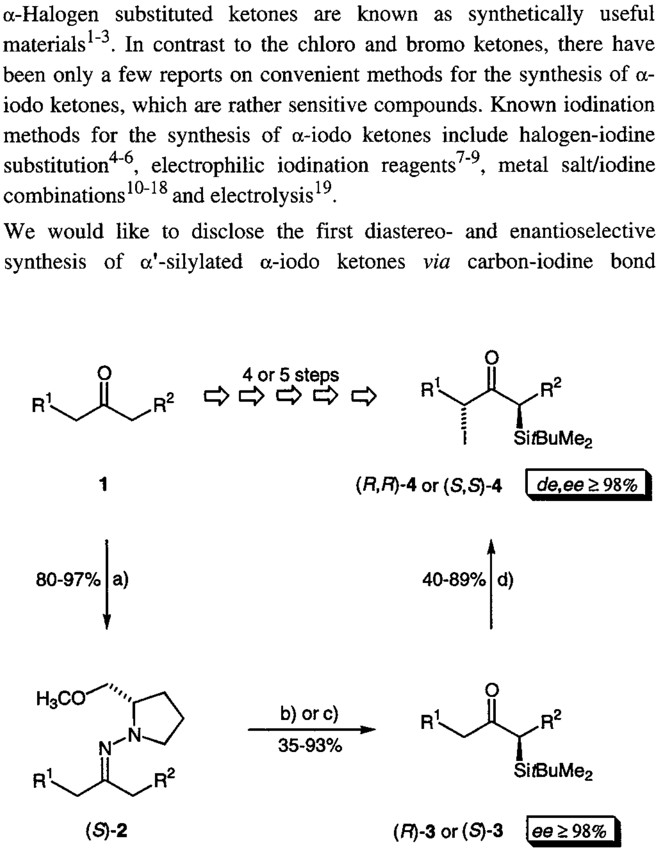
Abstract: The diastereo- and enantioselective syntheses of various α'-*t*-butyldimethylsilyl-α-iodo ketones **4a-h** is described. The carbon iodine bond formation is achieved using trifluoroiodomethane as the electrophilic iodination reagent. The iodo ketones **4** are obtained in good yields and with excellent diastereo- and enantiomeric excesses (*de,ee* ≥ 98%).

α-Halogen substituted ketones are known as synthetically useful materials[1-3]. In contrast to the chloro and bromo ketones, there have been only a few reports on convenient methods for the synthesis of α-iodo ketones, which are rather sensitive compounds. Known iodination methods for the synthesis of α-iodo ketones include halogen-iodine substitution[4-6], electrophilic iodination reagents[7-9], metal salt/iodine combinations[10-18] and electrolysis[19].

We would like to disclose the first diastereo- and enantioselective synthesis of α'-silylated α-iodo ketones *via* carbon-iodine bond formation with trifluoroiodomethane as electrophilic iodination reagent. As shown in Scheme 1, starting from simple ketones **1** enantiomerically pure α-*t*-butyldimethylsilyl ketones **3** were synthesized in three to four steps based on our SAMP/RAMP-hydrazone method[20-22]. Using symmetrically substituted ketones **1** as starting material the (*R*)-enantiomers of the α-silyl ketones **3** are obtained in three steps, whereas use of unsymmetrical ketones as starting materials led to the respective (*S*)-enantiomers of **3** in four steps with high enantiomeric excesses (*ee* ≥ 98%). The diastereoselective iodination of the chiral α-*t*-butyldimethylsilyl ketones **3** with trifluoroiodomethane afforded the α'-*t*-butyl-dimethylsilyl-α-iodo ketones **4**.



3-4	a	b	c	d	e	f	g	h
R^1	$-(CH_2)_4-$	Me	Me	Me	Et	Et	*n*-Pr	*n*-P
R^2		Me	*p*-Br-Bn	$BnCH_2$	*p*-Br-Bn	$BnCH_2$	*p*-Br-Bn	BnCl

a) SAMP, 60°C, neat

b) For symmetrical ketones (R^1=R^2):
1) LDA, THF, 0°C; *t*$BuMe_2SiOTf$, −78°C→rt 2) O_3, pentane, −78°C: → (*R*)-**3**

c) For unsymmetrical ketones (R^2=H):
1) LDA, THF, 0°C; *t*$BuMe_2SiOTf$, −78°C→rt 2) LDA, THF, 0°C; R^2I, −78°C→rt 3) O_3, pentane, −78°C: → (*S*)-**3**

d) LDA, THF, 0°C; CF_3I-THF-solution (inverse addition), −100°C→rt: (*R*)-**3** → (*R,R*)-**4**, (*S*)-**3** → (*S,S*)-**4**

Scheme 1

For carbon-iodine bond formation the enantiopure α-silyl ketones **3** were deprotonated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0°C. After cooling to −100°C the enolate was dropped into a solution of trifluoroiodomethane in THF at the same temperature *via* cannula (inverse addition). After aqueous workup the α'-*t*-butyldimethylsilyl-α-iodo ketones **4** were isolated in good yields (40-89%) and with excellent diastereo- and enantiomeric excesses (*de,ee* ≥ 98%, Table 1)[23].

Table 1. Asymmetric synthesis of α'-*t*-butyldimethylsilyl-α-iodo ketones **4**

4	R^1	R^2	yield 3→4 [%]	$[\alpha]_D^{22}$ (c, $CHCl_3$)	de^a,*ee* [%]	confg.
a	$-(CH_2)_4-$		47	−40.1 (1.00)	≥98	(*R,R*)
b	Me	Me	85	+229.5 (1.44)	≥98	(*R,R*)
b[b]	Me	Me	89	−239.5 (1.56)	≥98	(*S,S*)
c	Me	*p*-Br-Bn	69	−169.3 (0.90)	≥98	(*S,S*)
d	Me	$BnCH_2$	45	−192.6 (1.37)	≥98	(*S,S*)
e	Et	*p*-Br-Bn	76	−97.9 (1.10)	≥98	(*S,S*)
f	Et	$BnCH_2$	87	−138.0 (0.69)	≥98	(*S,S*)
g	*n*-Pr	*p*-Br-Bn	42	−58.2 (0.44)	≥98	(*S,S*)
h	*n*-Pr	$BnCH_2$	40	−168.0 (0.87)	≥98	(*S,S*)

[a] Diastereomeric excesses were determined by ^1H- and ^{13}C-NMR spectroscopy (500 MHz).

[b] RAMP was used as chiral auxiliary

Both enantiomers of the α'-*t*-butyldimethylsilyl-α-iodo ketones **4** can be obtained at will as is shown for the products (*R,R*)- and (*S,S*)-**4b** by using SAMP or RAMP as chiral auxiliary. The diastereomeric excesses of the iodo ketones **4** were determined by ^1H- and ^{13}C-NMR spectroscopy. The absolute configuration of compound (*S,S*)-**4e** was determined by X-ray crystal structure analysis[24]. Furthermore, the relative configurations of the new generated stereogenic centres of the title compounds **4a-h** were confirmed by extensive NOE experiments.

The virtually complete diastereofacial selectivity observed for iodination of compounds **3** is apparently due to the sterically demanding α-silyl group and the (*E*)-geometry of the lithium enolate generated. Thus, the (*R*)-configured silyl ketones **3** gave rise to the (*R,R*)-**4** products and (*S*)-**3** led to (*S,S*)-**4**, respectively.

In summary, an efficient asymmetric synthesis of α'-*t*-butyldimethylsilyl-α-iodo ketones **4** in good yields and with excellent diastereo- and enantiomeric excesses (*de,ee* ≥ 98%) has been developed, employing the commercially available trifluoromethyl iodide as iodinating reagent. Work is currently in progress to effect the carbon silicon bond cleavage to access virtually enantiopure α-iodo ketones for the first time as well as subsequent stereoselective reactions of the carbonyl and iodo groups.

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(23) *Synthesis of α'-t-butyldimethylsilyl-α-iodo ketones* ***4a-h**:*
The α'-*t*-butyldimethylsilyl ketones **3** (5 mmol) were added to a solution of LDA (6.5 mmol) in dry THF (50 mL) at 0°C. After 4h at 0°C the reaction mixture was cooled to −100°C and added to a solution of trifluoromethyl iodide (19.5 mmol) in dry THF (50 mL) *via* cannula at −100°C. After warming to room temperature overnight and aqueous work up (NH_4Cl-solution, Et_2O, $MgSO_4$) the α'-*t*-butyldimethylsilyl-α-iodo ketones **4** were purified by flash chromatography (SiO_2, ether/petroleum ether 1/1) and HPLC (Lichrosorb®, Merck, 25cm, 25mm, Si60, 7μm, ether/petroleum ether 5/95).
1-*p*-Bromophenyl-2-*t*-butyldimethylsilyl-4-iodohexane-3-one **4e**: yellow crystals, mp = 59-60°C. IR (KBr) 1680 cm^{-1} (C=O). ^1H NMR (500 MHz, $CDCl_3$): $\delta = -0.003$ (s, 3H, $SiC\underline{H}_3$), 0.11 (s, 3H, $SiC\underline{H}_3$), 0.95 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 0.99 (s, 9H, $C(C\underline{H}_3)_3$), 1.56-1.67 (m, 1H, $C\underline{H}_2CH_3$), 1.79-1.90 (m, 1H, $C\underline{H}_2CH_3$), 2.69 (dd, J = 13.5/2.0 Hz, 1H, $C\underline{H}_2CHSi$) 3.01 (dd, J = 12.1/2.0 Hz, 1H, $C\underline{H}_2CHSi$), 3.27 (dd, J = 13.7/11.9 Hz, 1H, $C\underline{H}Si$), 4.20 (dd, J = 9.7/4.0 Hz, 1H, $C\underline{H}I$), 7.04 (d, J = 8.0 Hz, 2H, $C\underline{H}_{ar}$), 7.36 (d, J = 8.4 Hz, 2H, $C\underline{H}_{ar}$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -6.90$ ($\underline{C}H_3$), −5.52 ($\underline{C}H_3$), 14.26 ($\underline{C}H_3$), 18.15 ($\underline{C}_{quart}$), 26.79 ($\underline{C}H_2$), 26.87 ($C(\underline{C}H_3)_3$), 33.24 ($\underline{C}H_2$), 38.71 ($\underline{C}HI$), 44.59 ($\underline{C}HSi$), 119.96 $Br\underline{C}_{quart}$)130.99 ($\underline{C}H_{ar}$), 131.26 ($\underline{C}H_{ar}$), 139.98 ($\underline{C}_{quart}$), 202.77 ($\underline{C}$=O). MS, m/z = 438.9 ($M^{+\cdot}$–*t*-Bu). HRMS Calcd. for $C_{14}H_{19}{}^{79}Br^{127}IOSi$: 436.9433, found: 436.9436.

(24) Details of the crystal structure investigation may be obtained from the Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, GB-Cambridge CB2 1EZ; Tel.: Int. +1223/336-408, Telefax: Int. +1223/336-033; E-mail: deposit@chemcrys.cam.ac.uk; World Wide Web: http://www.ccdc.cam.ac.uk.