Enantiocontrolled Synthesis of Optically Pure 5-Trimethylsilyl- and 5-Tributylstannyl-cyclohex-2-enones

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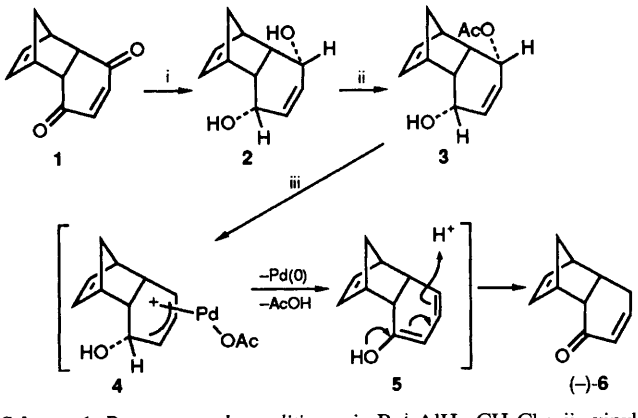
Optically pure 5-trimethylsilyl- and 5-tributylstannyl-cyclohex-2-enones have been prepared efficiently in an enantiocontrolled manner starting from the common chiral precursor by employing a novel palladium-mediated elimination reaction as the key step.

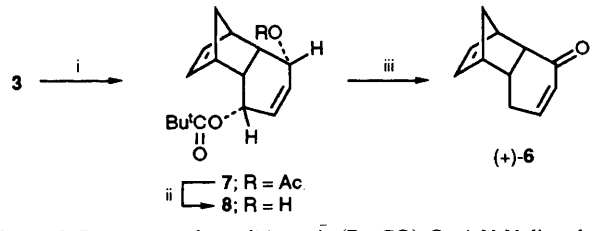
Both β-keto-silyl and β-keto-stannyl compounds, especially, the cyclic derivatives, are valuable intermediates for organic synthesis.[1] However, exploitation of these compounds in chiral synthesis has not been carried out fully owing to their difficult acquisition in optically pure states. We report here an efficient enantiocontrolled synthesis of potential chiral building blocks, 5-trimethylsilyl-[2] and 5-tributylstannyl-cyclohex-2-enones, in both enantiomeric forms starting from the common chiral precursor[3] **3** by employing the novel palladium-mediated elimination reaction as the key step.

Treatment of the *meso*-diol **2**, obtained *via* **1** by the sequential Diels–Alder reaction of cyclopentadiene and benzoquinone and reduction with diisobutylaluminium hydride (DIBAL), with vinyl acetate (6 equiv.) and lipase PS (Amano) in acetonitrile (30 °C, 2 weeks) afforded the optically pure monoacetate[3] **3** m.p. 87–88 °C, $[\alpha]_D^{31}$ + 72.2 (*c* 1.00, $CHCl_3$), in 87% yield. Anticipating to generate either the homoallylic or the allylic alcohol by hydrogenolytic removal of the acetoxy group, we treated **3** with ammonium formate (1.2 equiv.) in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium(II) (1 mol%) in dioxane at refluxing temperature.[4] The reaction was completed within 20 min, but the optically pure product obtained in 77% yield was found to be the unexpected α,β-unsaturated ketone [(−)-**6**], $[\alpha]_D^{32}$ −277 (*c* 0.99, $CHCl_3$).† This rather surprising outcome may be reasoned by the sequential formation of the (π-allyl)palladium complex **4** and the conjugated dienol **5** from **3** and concomitant isomerization of the latter into the enone **6** under the reaction conditions.

In order to obtain the antipodal enone [(+)-**6**], **3** was first acylated with pivalic anhydride to form the mixed diester **7** which was then stirred with methanolic potassium carbonate to give the pivalate **8**,‡ m.p. 109 °C, $[\alpha]_D^{31}$ −52.8 (*c* 1.00,



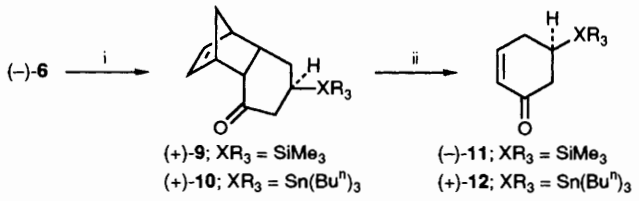
Scheme 1 *Reagents and conditions*: i, Bu^i_2AlH, CH_2Cl_2; ii, vinyl acetate, lipase PS, MeCN, 30 °C, 2 weeks; iii, $PdCl_2(PPh_3)_2$ (1 mol%), HCO_2NH_4 (1.2 equiv.), dioxane, reflux, 20 min



Scheme 2 *Reagents and conditions*: i, $(Bu^tCO)_2O$, 4-*N*,*N*-dimethylaminopyridine, NEt_3, CH_2Cl_2; ii, K_2CO_3, MeOH; iii, $PdCl_2(PPh_3)_2$ (1 mol%), HCO_2NH_4 (1.2 equiv.), dioxane, reflux, 20 min

† Optical purity was determined to be >99.5% enantiomeric excess (e.e.) by HPLC [Chiralcel OB, 5% Pr^iOH–hexane for (+)- and (−)-**6**; Chiralcel OJ, 0.2% Pr^iOH–hexane for (+)- and (−)-**11**].

‡ All new compounds except for **9** showed satisfactory analytical (combustion and/or high resolution mass) and spectral (IR, H NMR and mass) data.



Scheme 3 *Reagents and conditions*: X = Si: i, Me_3SiLi (3.4 equiv.), CuCN (1.7 equiv.), THF–HMPA (5:1), −30 °C; ii, diphenyl ether, 220 °C, 20 min; X = Sn: i, Bu^nLi (2.4 equiv.), CuCN (1.2 equiv.), Bu^n_3SnH (2.4 equiv.), THF, −78 °C; ii, diphenyl ether, 200 °C, 1 h, THF = tetrahydrofuran, HMPA = hexamethylphosphoramide

$CHCl_3$), in 82% overall yield, by selective removal of the acetoxy group. Upon the same treatment with the palladium catalysts as for **3**, **8** furnished the enantiomeric enone [(+)-**6**], $[\alpha]_D^{26}$ + 272 (*c* 1.00, $CHCl_3$) {lit.:[5] $[\alpha]_D^{18}$ + 261.0 (*c* 1.01, $CHCl_3$)}, in an optically pure state† in 81% yield without difficulty.

Owing to its biased framework, the tricyclic enone **6** allowed stereospecific 1,4-addition of a nucleophile from the convex face of the molecule. Thus, treatment of (−)-**6** with the trimethylsilylcuprate reagent,[6] generated from hexamethyldisilane with methyllithium followed by copper(I) cyanide, furnished the *exo*-trimethylsilyl ketone§ [(+)-**9**], m.p. 48–49 °C, in 83% yield as a single stereoisomer. The antipodal ketone§ [(−)-**9**], m.p. 48–49 °C, [lit.:[5] m.p. 48–50 °C], could also be obtained in a stereospecific manner in a comparable yield from (+)-**6** on the same treatment.

Quite similarly, treatment of (−)-**6** with the higher order tri-n-butylstannylcuprate reagent,[7] generated from tri-n-butylstannane with dilithium di-n-butylcopper(I) cyanide, afforded the *exo*-tri-n-butylstannyl ketone [(+)-**10**], $[\alpha]_D^{28}$ + 13.51 (*c* 1.38, $CHCl_3$), stereospecifically, in quantitative yield as a single stereoisomer. The antipodal ketone [(−)-**10**], $[\alpha]_D^{31}$ −13.61 (*c* 2.38, $CHCl_3$), could also be generated in a stereospecific manner in quantitative yield from (+)-**6**.

§ Although present in a small amount, this product was accompanied by an inseparable saturated by-product bearing an extra trimethylsilyl group which could be removed readily in the following retro-Diels–Alder cleavage.

Thermolysis of both enantiomers of the silyl ketone **9** and the stannyl ketone **10** at 200–220 °C in diphenyl ether initiated retro-Diels–Alder cleavage to generate the corresponding 5-substituted cyclohexenones, **11** and **12**, within an hour by removal of cyclopentadiene, respectively. Thus, (+)-**9** furnished (−)-**11**, $[\alpha]_D^{30}$ −9.06 (*c* 1.66, $CHCl_3$),† b.p. 115 °C at 17 mmHg (Kugelrohl) {lit.:[8] $[\alpha]_D^{20}$ −9.46 (*c* 1.40, $CHCl_3$), b.p. 65.5–67 °C, 2 mmHg (Kugelrohl)} and (+)-**11**, $[\alpha]_D^{20}$ + 8.89 (*c* 1.01, $CHCl_3$)],† b.p. 115 °C at 17 mmHg (Kugelrohr), in yields of 85 and 90%, respectively. Similarly, (+)-**10** furnished (+)-**12**, $[\alpha]_D^{25}$ + 7.01 (*c* 0.54, $CHCl_3$),† and (−)-**10** furnished (−)-**12**, $[\alpha]_D^{27}$ −7.04 (*c* 0.53, $CHCl_3$),† in yields of 85 and 88% after purification by silica gel column chromatography.

Utilization of the optically pure silyl and stannyl ketones as well as an extension of the palladium-mediated elimination reaction are currently under investigation.

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