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Synthesis of Optically Active 1-t-Butyl-4-ethylidenecyclohexane via CO_2-Elimination from a Spirofused β-Lactone

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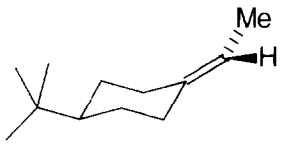
Key Words: (*R*)-1-t-Butyl-4-ethylidenecyclohexane, diastereoselectivity, chiral auxiliary, imidazolidin-2-one, aldolisation, β-lactone formation, CO_2 elimination.

Abstract: (*R*)-1-t-Butyl-4-ethylidene cyclohexane ((*R*)-**1**) is prepared with >98% ee from 4-t-butylcyclohexane carboxylic acid *via* the optically active β-lactone **10**.



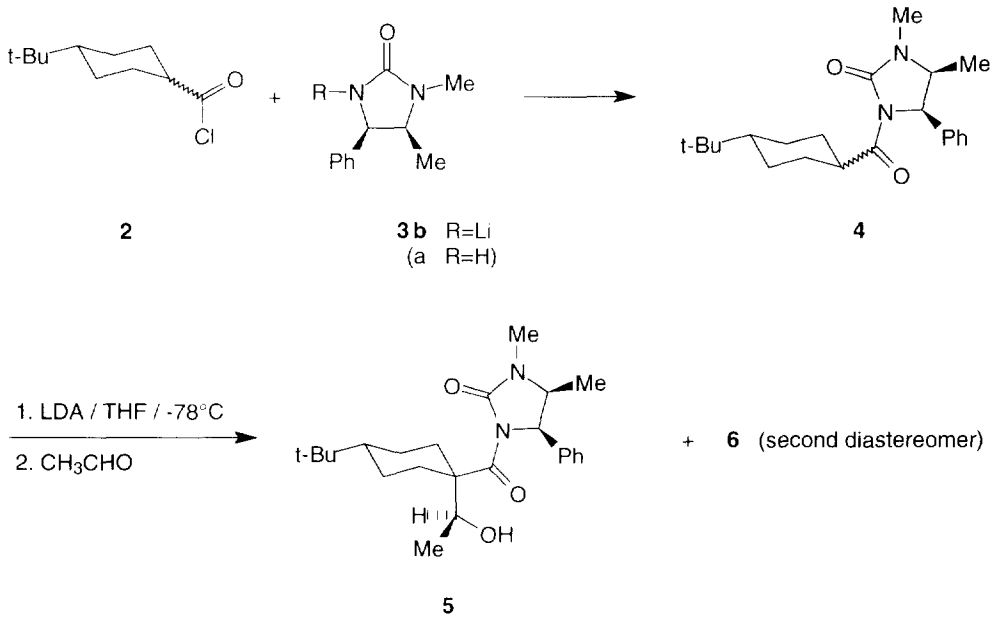
(*R*)-**1**

Fig. 1.

The synthesis of axially chiral olefins for instance 1-t-butyl-4-alkylidenecyclohexanes has attracted much attention over the past decade[1-4]. The ethylidene derivative **1** has been prepared in non-racemic form by three groups so far. Hanessian et al.[1] used optically active phosphonates for the synthesis of (*R*)-**1** from 4-t-butylcyclohexanone via Horner olefination, whereas Gais et al.[2] prepared (*S*)-**1** by a nickel catalysed cross coupling of dimethylzinc and the corresponding optically pure alkenylsulfoximine. Halterman et al.[3], finally, obtained (*S*)-**1** by catalytic isomerisation of achiral trans-4-t-butyl-1-vinyl-cyclohexane with a chiral titanium catalyst. Only the method by Gais furnished **1** in a satisfactory optical purity (ee 98%)[2].

We describe a simple route to olefin (*R*)-**1** with an ee of >98% (Scheme 1). Acid chloride **2** (cis-trans mixture) is converted into the amide **4** by treatment with the N-lithium-imidazolidinone **3b**[5]. Aldol addition of **4** to acetaldehyde furnishes two diastereomers **5** and **6** in a ratio of 90:10 and a combined isolated yield of 35%. By chromatography **5**, **6** and unchanged amide **4** are readily separated [R_F-values (ethyl acetate, hexane 1:1) silicagel: **5** (0.30), **6** (0.19), **4** (0.51)].

By recycling the reisolated amide **4** the effective yield of **5** is raised to about 70% in two successive runs. Possibly the diastereoselectivity can even be improved by means of Evans' enolborinate methodology[6]. Nevertheless, gram quantities of pure crystalline **5** can be procured via the route in its present state.

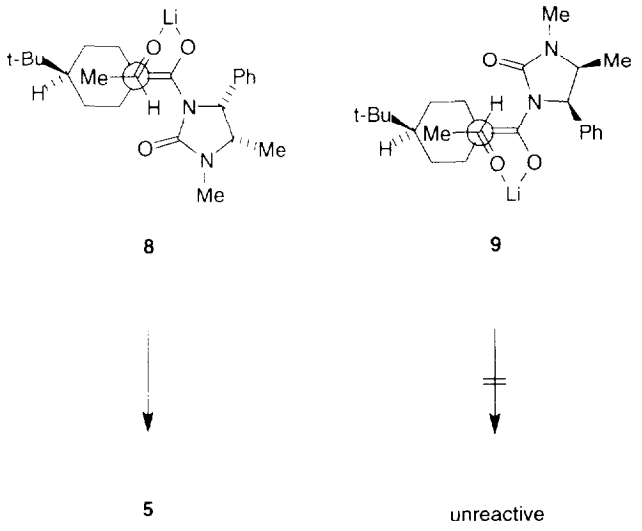


Scheme 1.

The structure of **5** has been clarified by an X-ray crystal structure analysis (Fig. 2)[7], whereas the configuration of **6** is unknown.

Fig. 2. Crystal Structure of **5**

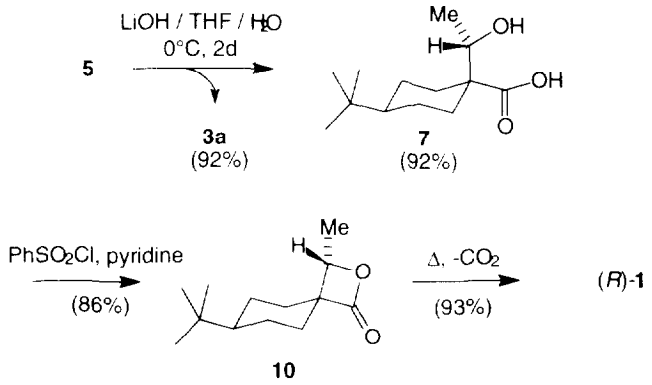
The stereochemical course of the formation of **5** may be rationalised (Scheme 2) by assuming that amide **4** is deprotonated to the two configurationally stable axially diastereomeric enolates shown in formulae **8** and **9**. The attack of the aldehyde occurs from the axial direction, which is unusual[8] and may be understood in terms of product development control[9], as the bulky amide sidechain surely has a strong tendency to adopt the equatorial position as soon as possible.



Scheme 2.

As a consequence of the 'axial' preference, the aldehyde approaches the enolate from the face opposite to the methyl and phenyl substituent in action complex **8**. This leads to a sterically favorable ('matched') situation. In arrangement **9** the attack occurs on the face syn to methyl and phenyl, which creates an unfavorable ('mismatched') situation; most likely arrangement **9** is not reactive at all which might explain the fact that 60% of the starting material is recovered unchanged. It is reasonable to assume that in **8** the aldehyde is attacked from its re-face to avoid a steric interaction of the aldehyde methyl group with the imidazolidinone oxygen.

Saponification of **5** generates the hydroxy acid **7** under quantitative recovery of the chiral auxiliary **3a** (Scheme 3).



Scheme 3.

Lactonisation with benzenesulfonyl chloride furnishes the stable β-lactone **10** which eliminates carbon dioxide on heating to 160 °C to give (*R*)-**1** in high yield. The enantiomeric purity of the olefin was analysed by chiral GC[10,11] which shows base line separation for the racemate and ee-values between 98% and 99.5% for our

samples of (*R*)-**1**. This means that the decarboxylation of the β-lactone **10** proceeds with complete retention of configuration as usual[12]. In conclusion, we have found an efficient route to optically pure **1**, which provides gram quantities of the product[13]. Apparently, our method creates axial chirality by combining two independent stereochemical elements, namely the axial-equatorial dichotomy on one hand and the formation of two diastereomeric enolates with different reactivity on the other hand. This provides the possibility of achieving matched and mismatched arrangements, and hence, of kinetic resolution in favor of reaction mode **8**.

As the chiral auxiliary **3a** is available also in its enantiomeric form, the synthesis furnishes (*S*)-**1** equally well. It should be applicable to other axially chiral olefins with small modifications. An alternative approach entails β-lactone formation from t-butylcyclohexanone and chiral propionate enolates. This route is also actively pursued in our laboratory.

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5. This auxiliary was chosen, because we observed an acyl migration with Evans' oxazolidinone converting the primary aldol adduct into an oxazinedione derivative (cf. A.S. Kende, K. Kawamura, M.J. Orwat, Tetrahedron Lett. **1989**, 30, 5821-5824, who report an analogous rearrangement). This oxazinedione was very hard to saponify with alkali.
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7. Summary of crystal data of **5** and data collection: Formula: $C_{24}H_{36}N_2O_3$, formula weight: 400.56 (g/mol), monocline, space group: $P2_1$, Z = 2, lattice constants: a = 11.321 Å, b = 7.142 Å, c = 14.550 Å, cell volume: 1127.2 Å^3, no. of electrons in unit cell, F (000): 436, density, d_{calc}: 1.180 g/cm^3, crystal size: 0.92 x 0.69 x 0.65 mm, radiation: MoKα, Nb filter, wavelength: 0.71068 Å, linear absorption coeff.: 0.77 cm^{-1}, temperature: 20 °C, data collection instrument: SIEMENS four circle diffractometer, orientation reflections no.: 140, range (2Θ(deg)): 34.0 - 47.7, scan method, steps (deg): ω-2Θ, 0.02-0.04, scan width (deg).Δω = 0.90 + 0.52 tan ω, no. of reflections collected: 4721, no. of unique reflections, R_{int}: 3528, no. of unique reflections with $F_o > 4\sigma(F_o)$: 2998, least-square refinement: full-matrix least-squares on F^2, function minimised: $\Sigma w (|F_o|^2 - |F_c|^2)^2$, no. of parameters refined: 406, final R: 0.0390 ($F_o > 4\sigma(F_o)$), wR2: 0.1183 (all data), goodness of fit, S: 1.046.
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10. Conditions: 25 m Chiralsil - Dex CB (0.25/0.25), 80 °C (35.5 min) with 70°C/min to 100°C, 0.7 bar hydrogen, retention time for (*R*)-**1** 35.85 min, (*S*)-**1** 36.09 min.
11. We thank C. Wienhold, G. Baude, S. Koschig, Schering AG Berlin for performing the chiral GC analysis.
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13. Analytical data: of **5**, **10**, **7** and (*R*)-**1**:
    5 : m.p. = 171-173 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.44-7.10 (5H, m, C_6H_5), 5.52 (1H, d, J = 9.5 Hz, C<u>H</u>-Ph), 5.32 (1H, d, J = 9.75 Hz, OH), 4.03 (1H, mc, C<u>H</u>-Me), 3.87 (1H, mc, C<u>H</u>-OH), 2.85 (3H, s, N-CH_3), 1.88-0.93 (9H, m, cyclohexane H), 1.09 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$-C-OH), 0.83 (9H, s, tBu), 0.78 (3H, d, J = 6 Hz, CH_3-C-NMe) ppm; $[\alpha]_D^{20}$ = -55.36 (589 nm, c = 1.12, $CHCl_3$).
    7 : m.p. = 131-133 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38-6.70 (2H, OH),4.13 (1H, q, J = 6.25 Hz, C<u>H</u>-OH), 2.40 (1H, mc, ring H), 1.85 (2H, mc, ring H), 1.68 (2H, mc, ring H), 1.56-1.33 (2H, m, ring H), 1.27 (3H, d, J = 6.25 Hz, CH_3), 1.07 (2H, mc, ring H), 0.84 (9H, s, tBu) ppm;$[\alpha]_D^{20}$ = -19.41 (589 nm, c = 1.19, $CHCl_3$).
    10 : m.p. = 70-71 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.49 (1H, q, J = 6.5 Hz, C<u>H</u>-Me), 2.08 (2H, mc, ring H), 1.80 (3H, mc, ring H), 1.69-1.58 (1H, m, ring H), 1.54 (3H, d, J = 6.25 Hz, CH_3), 1.17-0.89 (3H, m, ring H), 0.85 (9H, s, tBu) ppm.
    (R)-**1** : ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.14 (1H, q, J = 6.5 Hz, C<u>H</u>-Me), 2.69 (1H, mc, ring H), 2.23 (1H, mc, ring H), 2.00 (1H, mc, ring H), 1.91-1.78 (2H, m, ring H), 1.67 (1H, mc, ring H), 1.58 (3H, d, J = 6.5 Hz, CH_3), 1.30-0.90 (3H, m, ring H), 0.86 (9H, s, tBu) ppm; $[\alpha]_D^{20}$ = -17.76 (589 nm, c = 1.695, $CHCl_3$).

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