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Serendipitous synthesis of a ditwistane: a one-step access!

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Abstract—4-*tert*-Butyl-2-cyclohexen-1-one dimerizes in THF solution via its kinetic enolate, leading to di-*tert*-butylditwistane **8** in up to 36% yield (−78 °C → room temp., protonolysis, flash chromatography). X-ray crystallography shows that **8** incorporates one *R* and one *S* enantiomer of the starting ketone; none of the diastereomeric ditwistanes *epi*-**8**, *epi*'-**8** or *iso*-**8** was isolated. This means that the formation of **8** proceeds with mutual kinetic resolution and 100% induced diastereoselectivity.

Twistanes comprise the unsubstituted 1;4,2;5-bis(ethano)cyclohexane **1** and derivatives thereof; hence twistanes are tricyclic. Ditwistanes (**2**) are tetracyclic compounds and defined by the occurrence of a twistane substructure in which one cyclohexane ring is spanned—in a '*para*' manner—by a not yet accounted for (i.e., third) ethano bridge. Stated differently, ditwistanes consist of two twistanes, which have two twist-boat cyclohexane rings in common.

1

2

So far, to the best of our knowledge, there have been four syntheses of ditwistane(s) in the literature (vide infra): three accesses to the unsubstituted ditwistane **2**[1–3,4–6 and 3] and one synthesis of the dihydroxytetramethylditwistanedione **19**[7,8]. The fifth route to a ditwistane is the unexpected outcome of our recent attempt to effect a conjugate addition of tBu$_2$CuLi to 4-*tert*-butyl-2-cyclohexen-1-one (**3**; Scheme 1). Rather than the desired *trans*-3,4-di-*tert*-butyl-1-cyclohexanone ($C_{14}H_{26}O$) we isolated—according to HRMS—a product of molecular formula $C_{20}H_{32}O_2$ (36% yield).[9] The same compound $C_{20}H_{32}O_2$ resulted when 4-*tert*-butyl-2-cyclohexen-1-one (**3**) was treated with 0.6 equiv of KHMDS (30% yield). X-ray crystallographic analysis established that this compound was di-*tert*-butylhydroxyditwistanone **8**[10] (Fig. 1[11]).

Irrespective of the base, the overall transformation **3** → → **8** follows the same mechanism. As detailed in Scheme 1, it must comprise the following steps: partial enolate formation (→metalo-**3**); tandem[13] intermolecular/intramolecular Michael addition OR enolate Diels–Alder reaction[14] (→**4**); ketoenolate equilibration (**4**→**6**); aldol addition (→**7**); alcoholate protonation upon workup (→**8**).

Ditwistane **8** *with the indicated stereochemistry* results as the dimerization product of 4-*tert*-butylcyclohexenone (**3**) and its enolate (metalo-**3**) only if the introductory Michael addition (→**4**) proceeds with an effective mutual resolution (cf. Scheme 1): Along the ditwistane-delivering pathway, the *R*-enantiomer of the enolate and the *S*-enantiomer of the non-deprotonated enone combine exclusively with one another—and vice versa (which implies that *enantiopure* 4-*tert*-butylcyclohexenone cannot form ditwistane **8** upon partial deprotonation). The reason for this preference is the minimization of steric hindrance, plausibly while the first C–C bond forms: Only said mutual reconnaissance allows each

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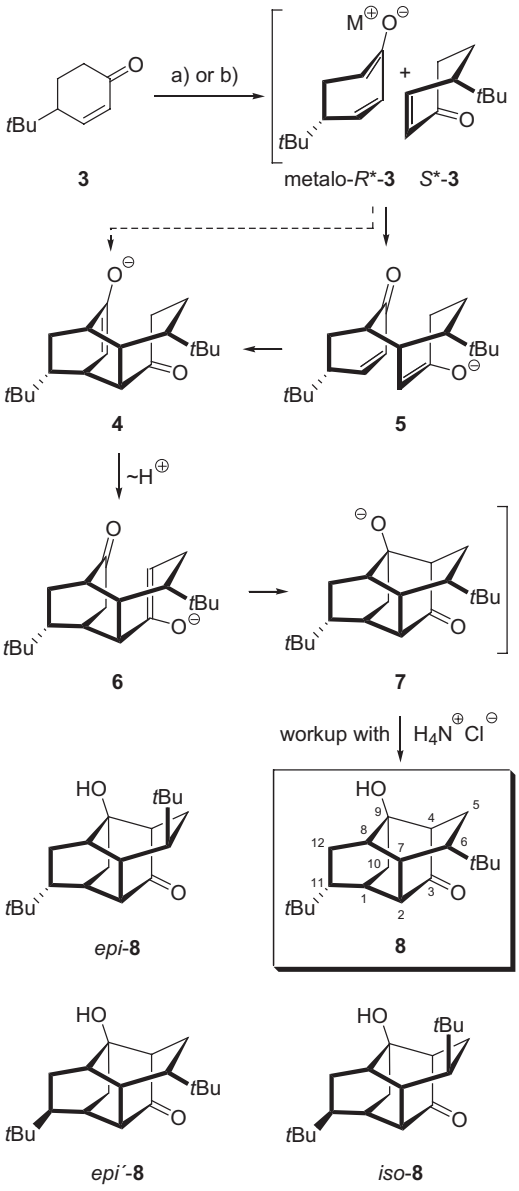


Scheme 1. Reagents and conditions: (a) $t\text{Bu}_2\text{CuLi}$ (2.0 equiv), Et_2O, −30 °C, 30 min, room temp., 21 h; 36% (we re-isolated a considerable amount of impure **3** implying 'considerably more than 36% yield of **8** based on recovered starting material'). (b) KHMDS (0.6 equiv), THF, −78 °C (25 min), room temp. (16 h); 33%.

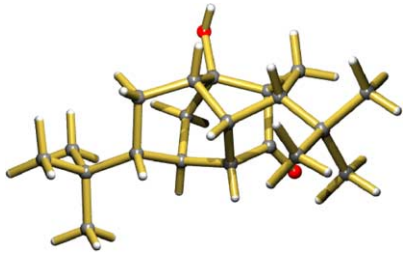
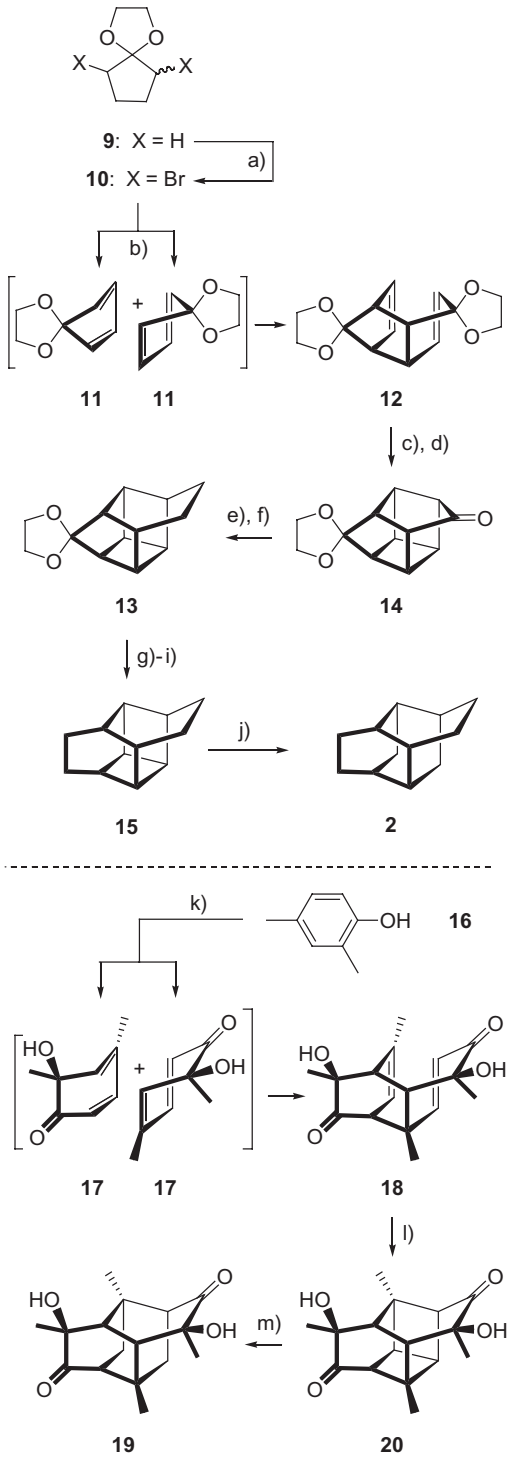


Figure 1. Pluton/Povray plot[12] of ditwistane **8**.

reactant to selectively engage *that* face of its six-membered ring, which *opposes* the attached *tert*-butyl substituent.

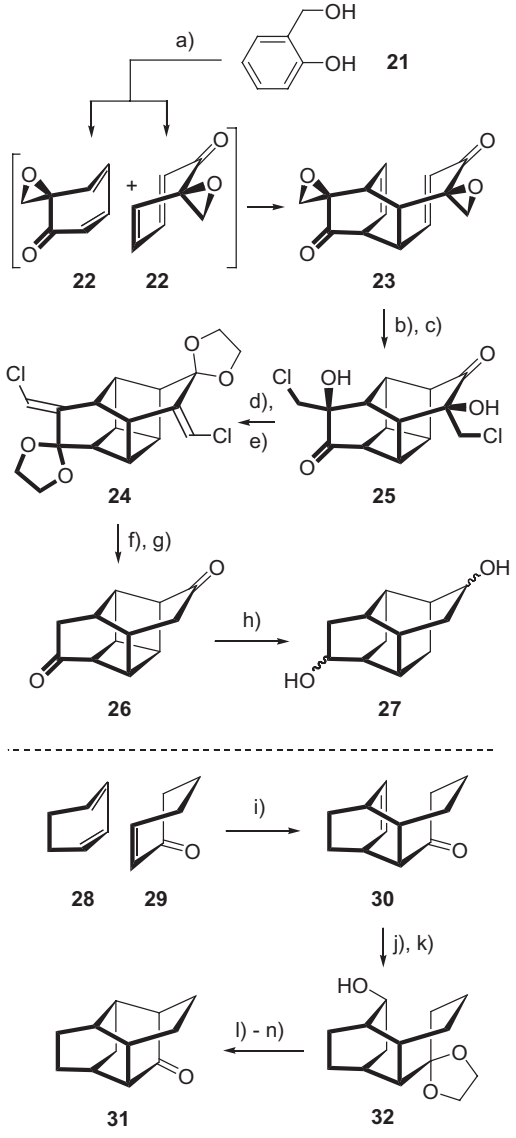
In contrast, if uniquely enolate metalo-**3** had reacted on the face *opposite* to its *tert*-butyl group, enone **3**, however, *on* its *tert*-butylated side, the epimeric ditwistane *epi*-**8** would have been obtained. Conversely, if enolate metalo-**3** had reacted *on* its *tert*-butylated side and enone **3** on the less hindered *opposite* side, another epimer



Scheme 2. Reagents and conditions: Ref. 1: (a) Br_2; 68%; (b) NaOMe, Δ; 69%; Ref. 2: (c) HCl, aq THF; 77%; (d) *hv*; 82%; Ref. 3: (e) CH_2N_2; (f) hydrazine hydrate, KOH, triethylene glycol; 85% over the two steps; (g) aq H_2SO_4; 90%; (h) CH_2N_2; (i) hydrazine hydrate, KOH, triethylene glycol; 73% over the two steps; (j) H_2, Pd/C; 77%.—Ref. 7: (k) $NaIO_4$, H_2O; ⩽20%; Ref. 8: (l) *hv*; 82%; (m) H_2, Pd/C; 92.5%.

would have resulted, namely ditwistane *epi*'-**8**. If, finally, bond formation between enolate metalo-**3** and enone **3** had occurred *on* the *tert*-butylated side of *both* reactants, this would have yielded compound *iso*-**8**, that is, another diastereomer—albeit not an epimer—of the actually formed ditwistane **8**. We detected none of these diastereomers during chromatography—assuming they would have eluted from the column with similar polarity as **8**.

Our synthesis of ditwistane **8** in 1 step and 36% yield is more straightforward and more efficient than the previously described approaches to the ditwistane framework: The route from acetal **9** to ditwistane **2** comprised 10 steps and provided 13% overall yield (Scheme 2, top);[1–3] the conversion of dimethylphenol **16** into the octasubstituted ditwistane **19** comprised three steps and afforded ⩽15% overall yield (Scheme 2, bottom);[7,8] the synthesis of the ditwistanediols **27**—as a mixture of stereoisomers—from *ortho*-(hydroxymethyl)phenol (**21**) required eight steps and afforded 5.4% overall yield (Scheme 3, top);[4–6] last but not least, the transformation of diene **28** and dienophile **29** into the ditwistanone **31** proceeded in six steps and gave 0.08% overall yield (Scheme 3, bottom).[3] It is noteworthy that the three last-mentioned syntheses and our access have one feature in common: The C_{12} scaffolds of the respective ditwistanes **19**, **27**, **31**, and **8** are established from two six-membered ring reagents.



Scheme 3. Reagents and conditions. Ref. 4: (a) $NaIO_4$, H_2O; 74%; Ref. 5: (b) HCl; 94%; (c) *hv*; 38%; Ref. 6: (d) ethylene glycol, *p*-TsOH; 94%; (e) $SOCl_2$, pyridine; 67%; (f) aq HCl; 90%; (g) aq KOH; 76%; (h) H_2, Pd/C; ⩾47%.—Ref. 3: (i) Diels–Alder reaction: hydroquinone, Δ; 6%; (j) ethylene glycol, *p*-TsOH; 78%; (k) B_2H_6; H_2O_2, NaOH; (l) 10% H_2SO_4; 25% over the two steps; (m) MsCl, pyridine; (n) NaH, DMF; 7% over the two steps.

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9. (1*R**,2*R**,4*R**,6*S**,7*S**,*S**,9*R**,11*R**)-6,11-Di-*tert*-butyl-9-hydroxytetracyclo[6.2.2.$0^{2,7}$.$0^{4,9}$]dodecan-3-one (**8**): Method A: At −70 °C *t*BuLi (1.5 M in pentane, 42 mL, 63 mmol, 4.0 equiv) was added to a suspension of CuI (6.068 g, 31.9 mmol, 2.0 equiv) in Et_2O (175 mL). After 30 min the temperature was raised to −30 °C and 4-*tert*-butyl-2-cyclohexen-1-one (2.419 g, 15.9 mmol) was added dropwise. The temperature was increased to ambient. After 21 h, quenching with 1:1 satd aq NH_4Cl/conc. aq NH_3 (350 mL), extractive workup, drying over $MgSO_4$, and flash chromatography on silica gel (cyclohexane/EtOAc 10:1 → 1:1) provided the title compound (0.867 g; 36%) as a colorless solid (mp 215–217 °C; recrystallization from toluene → X-ray crystallography). Earlier fractions of the chromatographic separation provided unidentified mixtures (0.564 g) followed by a dark oil (1.497 g) which, according to the 300 MHz ^{1}H NMR spectrum in $CDCl_3$ consisted mostly of re-isolated 4-*tert*-butyl-2-cyclohexen-1-one (<9.83 mmol, <62%). Method B: At −78 °C 4-*tert*-butyl-2-cyclohexen-1-one (200 mg, 1.31 mmol) in THF (4 mL) was added dropwise to KHMDS (158.2 mg, 0.793 mmol, 0.6 equiv) in THF (15 mL). After 25 min the cooling bath was removed. Sixteen hours later the reaction was quenched by adding satd aq NH_4Cl (14 mL) and the resulting mixture processed similarly as described above (the eluent being cyclohexane/EtOAc 7:2 → 2:1). This, too, afforded crystalline **8** (52.4 mg; 33%). ^{1}H NMR (500.1 MHz,C_6D_5H as internal standard in C_6D_6): δ = 0.73 and 0.79 [2s, 2 × C(CH_3)$_3$], 1.20 (br s, OH), 1.24 [$J_{8,12\text{-H(B)}}$ = 10.8, $J_{8,12\text{-H(A)}}$ = 8.2, $J_{8,7} \approx 0$ (cf. Ref. 10), 8-H*], 1.28–1.35 (m, 6-H, 10-H^1, 11-H*), superimposes high-field branch of A part of AB signal (δ_A = 1.39,

$\delta_B = 1.66$, $J_{AB} = 12.8$, in addition split by $J_{A,8} = 8.1$, $J_{A,11} = 4.9$, $J_{B,8} = 11.3$, $J_{B,11} = 1.2$, 12-H_2), B part of preceding signal interlocks with 1.63 [d, $J_{gem} = 12.5$, $J_{10\text{-}H(2),1} \approx 0$ (cf. Ref. 10), 10-H^2], AB signal ($\delta_A = 1.71$, $\delta_B = 2.04$, $J_{AB} = 14.1$, in addition split by $J_{A,4} = J_{A,6} = 3.2$, $J_{B,6} = 11.4$, $J_{B,4} = 2.5$, 5-H_2), 1.80 [dd, $J_{1,2} = J_{1,10\text{-}H(1)} = 6.0$, $J_{1,10\text{-}H(2)}$ and $J_{1,11} \approx 0$ (cf. Ref. 10), 1-H], 1.92 [dd, $J_{7,2} = 5.9$, $J_{7,6} = 2.8$, $J_{7,8} \approx 0$ (cf. Ref. 10), 7-H], 2.10 (br dd, $J_{4,5\text{-}H(A)} \approx J_{4,5\text{-}H(B)} \approx 2.8$, 4-H), 2.26 (dd, $J_{2,1} = J_{2,7} = 6.0$, 2-H); *assignments interchangeable. ^{13}C NMR [125.7 MHz, C_6D_6; 1. ^{1}H decoupled; 2. APT ("+" for upward and "−" for downward peaks)]: δ="+" 23.39 (C-12), "+" 24.67 (C-5), "−" 28.03 and "−" 28.77 [6-C(CH_3)$_3$ 11-C(CH_3)$_3$], 30.16,* 32.75,* and 33.25* [6-C(CH_3)$_3$, 11-C(CH_3)$_3$, C-11**], "−" 31.05 (C-1), "+" 34.85 (C-10), "−" 38.36 (C-7), "−" 43.40 (C-8**), "−" 47.21 (C-6), "−" 50.22 (C-2), "−" 59.72 (C-4), 73.88* (C-9), 215.05* (C-3); *signal not detected in APT ^{13}C NMR spectrum after 40,960 scans of a satd sample; **assignments interchangeable if and when assignments of 8-H/11-H are changed (vide supra). IR (film): $\tilde{\upsilon} = 3380$, 2960, 2925, 2875, 1705, 1480, 1395, 1370, 1330, 1315, 1290, 1240, 1200, 1175, 1150, 1120, 1065, 1020 cm^{-1}. MS (EI, 70 eV): m/z = 304 (11%, $M^{\bullet\oplus}$), 289 (2%, $M^{\bullet\oplus}$–$Me^{\bullet}$), 247 (2%, $M^{\bullet\oplus}$–tBu$^{\bullet}$), 153 (30%, $C_{10}H_{17}O^{\oplus}$ = 4-*tert*-butyl-1-hydroxy-1-cyclohexen-3-yl$^{\oplus}$), 152 (100%, $C_{10}H_{16}O^{\bullet\oplus}$ = 4-*tert*-butyl-2-cyclohexen-1-one$^{\bullet\oplus}$), 96 (98%, $C_6H_8O^{\bullet\oplus}$ = 3-cyclohexen-1-one$^{\bullet\oplus}$ = McLafferty product of m/z = 152), 57 (72%, $C_4H_9^{\oplus} = t$Bu$^{\oplus}$). Elemental analysis calcd (%) for $C_{20}H_{32}O_2$ (304.5): C 78.90, H 10.61; found C 78.73, H 10.59.

10. Compound **8** comprises two isolated ^{1}H spin systems: 10-H_2 ⟺ 1-H ⟺ 2-H ⟺ 7-H ⟺ 6-H ⟺ 5-H_2 ⟺ 4-H and 8-H ⟺ 12-H_2 ⟺ 11-H. This results from the virtual absence of vicinal couplings between 1-H and 11-H ($J_{1,11} \approx 0$ Hz) and between 7-H and 8-H ($J_{7,8} \approx 0$ Hz). In the Karplus analysis, the smallness of these couplings reflects the proximity of the corresponding torsional angles to 90° as calculated from the X-ray data: ∠1-H/C-1/C-11/11-H = 82.6°, ∠7-H/C-7/C-8/8-H = 78.4°. Similarly, $J_{1,10\text{-}H(2)} \approx 0$ Hz is in accordance with the torsional angle ∠1-H/C-1/C-10/10-H(2) = 82.1° in the solid state. Since conversely ∠1-H/C-1/C-10/10-H(1) = 37.9° in the crystal and hence $J_{1,10\text{-}H(1)}$ larger (namely 6.0 Hz), the assignments 10-H(1) = 10-H(*si**) and 10-H(2) = 10-H(*re**) can be made.
11. CCDC 252042 contains the supplementary crystallographic data for this paper. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or http://deposit@ccdc.cam.ac.uk.
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