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A simple strategy for the synthesis of optically pure *trans*-hydrindane systems

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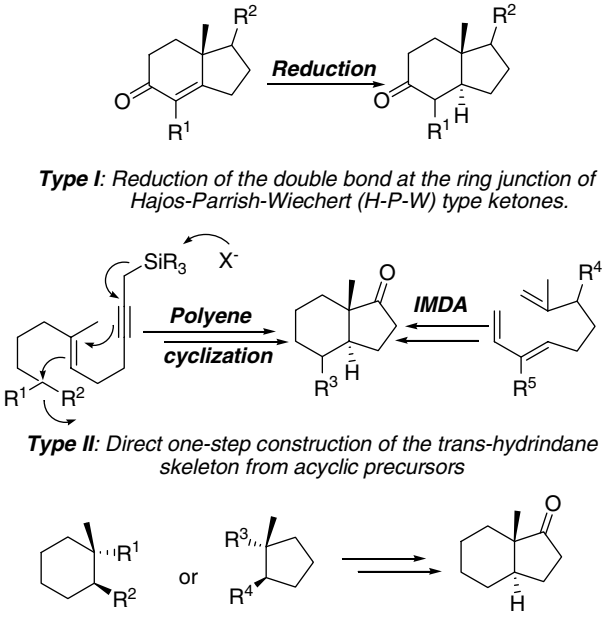
Abstract—A new strategy for the synthesis of optically pure *trans*-hydrindane systems is reported from an easily available starting material.

A multitude of bioactive natural products such as steroids, hormones, vitamin D, some of the higher terpenes and related natural products contain a *trans*-hydrindane moiety as a core structural feature.[1] In particular, the *trans*-hydrindane moiety of 1α,25-dihydroxyvitamin D_3, functionalized at C-12 is shown to modulate strongly, the affinity of the vitamin D receptors.[2a] Similarly, C-16 substituted 1α,25-dihydroxyvitamin D_3 is also known[2b] to alter the ligand–enzyme interactions causing significant slowing down of the rate of the enzymatic side-chain oxidation. Therefore, there has been intense research activity over the years towards developing a suitable synthetic strategy for the construction of substituted *trans*-hydrindane moieties.[1b,2b] The principal challenge in the synthesis of this moiety lies in the construction of *trans*-stereocenters at the ring junction. The known synthetic routes for the preparation of this moiety may be categorized into three classes as depicted in Scheme 1.



Scheme 1. Synthetic routes to the *trans*-hydrindane skeleton.

Although, stereoselective reduction of the double bond at the ring junction in Hajos–Parrish–Wiechert type ketones (type I approach)[3] represents one of the most explored strategies, the dependence of stereoselectivities on the stereoelectronic features of R^1 and R^2 limits its utility. The type II approaches, in which the *trans*-hydrindane skeleton is constructed in one-step directly from acyclic precursors either by polyene cyclization or an intramolecular Diels–Alder reaction (IMDA), suffer from low stereocontrol in general.[3] Furthermore, this strategy may not be suitable for the synthesis of functional derivatives of the hydrindane moiety. The best stereochemical control has been achieved through type III approaches involving stereoselective annulation of either cyclopentane over cyclohexane or vice versa. However, these approaches suffer from the difficulty of

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procuring suitably substituted six- or five-membered ring precursors.

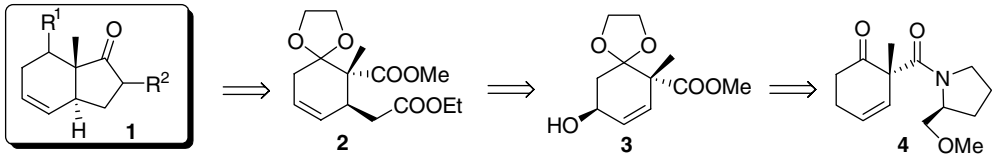
Therefore, considering the importance of the *trans*-hydrindane moiety and the difficulties encountered in its construction, we envisaged a common precursor **2** from which a range of structurally modified *trans*-hydrindane derivatives could be synthesized. The synthesis of **2** was envisioned from compound **4** (Scheme 2), easily obtainable from a cheap aromatic starting material using Schultz's asymmetric Birch reduction–alkylation protocol.[4] In this letter, we describe the success of our endeavors for developing a simple protocol for the synthesis of *trans*-hydrindane systems.

Our synthetic strategy began with the synthesis of a common precursor **2** from ketone **4**, readily available by the asymmetric Birch reduction–alkylation protocol (88% yield) developed by Schultz et al.[4] In this context, **4** was first converted to the corresponding dioxolane derivative **5**, which upon LAH reduction[5] produced the corresponding aldehyde **6** in 89% yield.[6] The chiral auxiliary was also recovered in 85% yield. Compound **6** was subsequently transformed to ester **7** by $NaClO_2$ oxidation followed by esterification using diazomethane. Allylic oxidation of **7** using PDC and *tert*-butylhydroperoxide[7] followed by reduction under Luche's conditions[8] gave the corresponding allylic alcohol **8** in 90% yield as a 1:1 diastereomeric mixture, as established by GC as well as ^1H NMR spectral studies. In order to transform this mixture of diastereomers into the pure *trans*-diastereomer, we first converted it into lactone **9**, which on methanolysis afforded the corresponding *cis*-isomer.[9] Mitsunobu inversion of this *cis*-isomer easily produced the desired *trans*-isomer **3** in 92% yield.[10] Subjecting **3** to the Johnson's orthoester Claisen rearrangement furnished diester **2** (93% yield), which possessed vicinal quaternary and tertiary stereocenters in the desired *trans*-fashion (Scheme 3).[11] The stage was now set for exploring the utility of **2** for the synthesis of varied structures of *trans*-hydrindane systems.

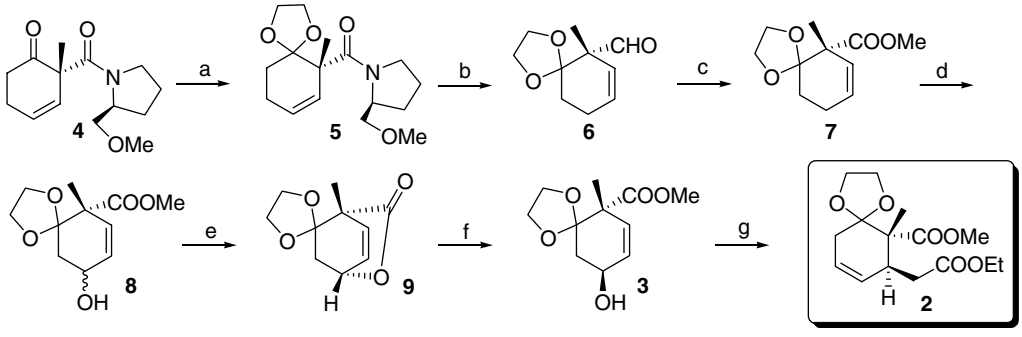
In order to synthesize *trans*-hydrindane derivative **15**, compound **2** was first subjected to one carbon homologation, employing the well-known Arndt–Eistert reaction, to give **14** in 78% yield. Dieckmann cyclization of **14** using NaHMDS in THF yielded the corresponding β-ketoester in 94% yield. Finally, demethoxycarbonylation of the β-ketoester was carried out by heating with DABCO in *o*-xylene[12] to afford the *trans*-hydrindane system **15** ($[\alpha]_D^{25}$ +7.38, *c* 0.8, CH_2Cl_2) in 82% yield.[13]

With the successful synthesis of **15**, we moved on to prepare compounds **13** and **17** using **2** as a common precursor. For the synthesis of **13**, substrate **2** was converted to the corresponding deoxygenated compound **11** via reduction of the corresponding dithiolane derivative **10** using $^nBu_3SnH$. Our initial experiment for the reduction of **10** by refluxing with $^nBu_3SnH$ and a catalytic amount of AIBN in benzene failed to yield any product. However, refluxing a neat mixture of **10** and $^nBu_3SnH$ with the addition of several small portions of AIBN over a period of 24 h furnished the desired compound **11** in 96% yield.[14] Conversion of **11** to **13** ($[\alpha]_D^{25}$ +5.625, *c* 0.16, CH_2Cl_2) was achieved in a similar manner as described for **15** (Scheme 4) earlier.[15]

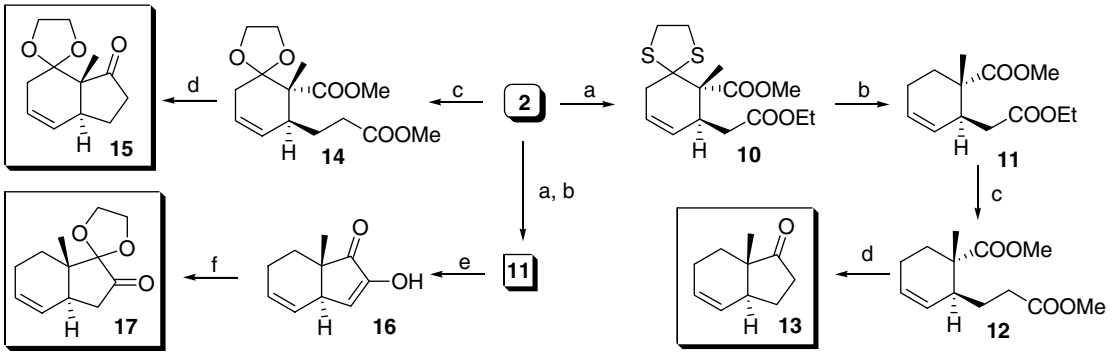
During the proposed conversion of compound **2** to **17** via acyloin condensation of **11**, it was anticipated that it would produce the *trans*-hydrindane system with an α-hydroxy ketone in the five-membered ring. However, when **11** was subjected to the acyloin condensation by



Scheme 2. Retrosynthetic strategy.



Scheme 3. Synthesis of common intermediate **2**. Reagents and conditions: (a) $(CH_2OH)_2$, *p*-TsOH, toluene, reflux, 98%; (b) LAH, THF, −20 to 0 °C, 89%; (c) (i) $NaClO_2$, H_2O_2, CH_3CN/H_2O (1:1.7), 0 °C to rt; (ii) CH_2N_2, Et_2O, 0 °C to rt, 95%; (d) (i) PDC, $^tBuO_2H$, DCM, 10 °C to rt, 68%; (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C to rt, 90%; (e) (i) LiOH, THF/H_2O (1.3:1), rt, 92%; (ii) $BF_3{\cdot}OEt_2$, DCM, 0 °C, 82%; (f) (i) NaOMe, MeOH, reflux, 96%; (ii) DIAD, PPh_3, BzOH, THF, 0 °C to rt; (iii) 1N NaOH, MeOH, rt, 92%; (g) $CH_3C(OEt)_3$, propionic acid, 137 °C, 93%.



Scheme 4. Synthesis of **13**, **15**, and **17**. Reagents and conditions: (a) (i) 10% HCl, THF, rt, 93%; (ii) ethanedithiol, $BF_3{\cdot}OEt_2$, DCM, 0 °C to rt, 97%; (b) $^nBu_3SnH$, AIBN, 130 °C, 96%; (c) (i) 1 equiv NaOH, MeOH, reflux, 87%; (ii) $SOCl_2$, pyridine, PhH, rt; (iii) CH_2N_2, Et_2O, 0 °C to rt; (iv) Ag_2O, MeOH, reflux, 78%; (d) (i) NaHMDS, THF, 0 °C to rt, 94%; (ii) DABCO, *o*-xylene, 150 °C, 82%; (e) Na, liq. NH_3, −78 °C, 63%; (f) $(CH_2OH)_2$, *p*-TsOH, toluene, 90 °C, 94%.

treatment with sodium in liquid ammonia at −78 °C, compound **16** was obtained as the major product and the expected α-hydroxy ketone was not produced in isolable amounts.[16] Therefore, compound **16** was subjected to dioxolane protection under controlled conditions (ethylene glycol, *p*-TsOH, toluene, 90 °C, 6 h) to afford **17** ($[\alpha]_D^{25}$ +6.27 (*c* 0.35, CH_2Cl_2)) as the sole product (Scheme 4).[17]

In summary, we have successfully developed a new approach for the stereoselective construction of *trans*-hydrindane systems, present in a large number of bioactive natural products and analogues starting from the readily accessible ketone **4**. The functionalities present at suitable positions provide the means for their conversion into more complex molecular entities. Further studies are in progress to utilize this strategy in the synthesis of some biomedically important compounds possessing vicinal quaternary and tertiary stereocenters in *trans*-fashion in cyclohexane ring systems.

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5. Addition of **5** to a slurry of LAH in THF led to the formation of the corresponding amine. Aldehyde **6** was obtained selectively by reverse addition of a slurry of LAH in THF to a stirred solution of **5** at low temperature (−20 °C).
6. Compound **6**: $[\alpha]_D^{25}$ −30.42 (*c* 0.76, $CHCl_3$); IR (film) ν_{max} 2957, 1724, 1454, 1361, 1245, 1099, 1026, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 3H), 1.79 (t, $J = 6.3$ Hz, 2H), 2.14–2.33 (m, 2H), 3.84–4.12 (m, 4H), 5.33 (dt, $J = 10.1$, 2.0 Hz, 1H), 5.88 (dt, $J = 10.2$, 3.5 Hz, 1H), 9.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4, 24.3, 28.4, 55.5, 64.7, 64.9, 109.4, 127.3, 128.9, 201.3; Anal. Calcd for $C_{10}H_{14}O_3$ (182.22): C, 65.91; H, 7.71. Found: C, 65.83; H, 8.00.
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10. Compound **3**: $[\alpha]_D^{25}$ −42.73 (*c* 0.68, CH_2Cl_2); IR (film) ν_{max} 3447, 2985, 1733, 1438, 1255, 1117, 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3H), 1.91 (dd, $J = 13.7$, 4.0 Hz, 1H), 2.46 (dd, $J = 13.7$, 5.2 Hz, 1H), 3.70 (s, 3H), 3.98–4.07 (m, 4H), 4.29–4.36 (m, 1H), 5.61 (dd, $J = 10.0$, 0.9 Hz, 1H), 5.90 (dd, $J = 9.8$, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.9, 38.6, 52.0, 55.7, 63.7 (2C), 68.9, 111.7, 131.5, 133.4, 165.8; GC–MS (*m*/*z*) 228 (M^+), 180, 166, 152, 137, 112, 107, 93, 74 (100), 60, 41; Anal. Calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.07. Found: C, 57.72; H, 6.95.
11. Compound **2**: $[\alpha]_D^{25}$ +21.70 (*c* 0.84, CH_2Cl_2); IR (film) ν_{max} 2996, 1736, 1730, 1633, 1440, 1371, 1250, 1053, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15 (t, $J = 7.1$ Hz, 3H), 1.54 (s, 3H), 2.12–2.56 (m, 5H), 3.72 (s, 3H), 3.89–4.08 (m, 4H), 4.22 (q, $J = 7.0$ Hz, 2H), 5.43–5.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.1, 22.0, 28.2, 34.4, 36.5, 52.3, 53.0, 63.7, 65.1, 65.4, 112.0, 121.4, 125.6, 173.9 (2C); GC–MS (*m*/*z*) 253 (M^+−OEt), 237, 227, 210, 195, 181, 169, 152, 151, 125, 107, 86, 79, 57 (100), 43; Anal. Calcd for $C_{15}H_{22}O_6$ (298.34): C, 60.39; H, 7.43. Found: C, 60.31; H, 7.23.
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13. Compound **15**: $[\alpha]_D^{25}$ +7.38 (*c* 0.8, CH_2Cl_2); IR (film) ν_{max} 2964, 1736, 1461, 1404, 1178, 1091, 1043, 910, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (s, 3H), 1.55 (t, $J = 6.3$ Hz, 2H), 1.85–2.11 (m, 3H), 2.17–2.37 (m, 1H), 2.52–2.71 (m, 1H), 4.11 (s, 4H) 5.54–5.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.2, 21.7, 24.6, 33.6, 38.4, 40.7, 65.8 (2C), 114.3, 125.7, 129.1, 221.7; GC–MS (*m*/*z*) 208 (M^+), 180, 165, 138, 126, 113, 94, 79, 67, 41; Anal. Calcd

for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.74. Found: C, 69.07; H, 7.91.

14. Compound **11**: $[\alpha]_D^{25}$ +12.4 (*c* 1.49, CH_2Cl_2). IR (neat film) ν_{max} 3022, 2983, 1730, 1654, 1448, 1373, 1247, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.10$ (s, 3H), 1.26 (t, $J = 7.0$ Hz, 3H) 1.55–1.80 (m, 2H), 1.85–2.20 (m, 4H), 2.25–2.50 (m, 1H), 3.70 (s, 3H), 4.13 (q, $J = 7.0$ Hz, 2H), 5.50 (dt, $J = 10.2$, 2.4 Hz, 1H) 5.67 (dd, $J = 10.2$, 2.4 Hz, 1H); ^{13}C ($CDCl_3$, 75 MHz) 13.7, 16.3, 21.6, 31.0, 35.7, 36.8, 43.5, 51.5, 60.0, 125.7, 128.0, 172.0, 177.4; GC–MS (*m*/*z*) 240 (M^+), 208, 194, 180, 166, 151, 135, 121, 107, 93, 74, 61, 41; Anal. Calcd for $C_{13}H_{20}O_4$ (240.30): C 64.98, H 8.39. Found C 65.23, H 8.24.
15. Compound **13**: $[\alpha]_D^{25}$ +5.63 (*c* 0.16, CH_2Cl_2); IR (film) ν_{max} 3020, 2927, 1735, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 3H,), 1.32–1.41 (m, 2H), 1.60–1.80 (m, 2H), 1.90–2.00 (m, 2H), 2.15–2.40 (m, 3H), 5.52–5.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 21.8, 26.2, 27.0, 35.9, 43.6, 47.2, 127.5, 129.0, 223.4; GC–MS (*m*/*z*) 151 (M^++1), 137, 110, 109, 95, 79, 57, 41; Anal. Calcd for $C_{10}H_{14}O$ (150.22): C, 79.96; H, 9.39. Found: C, 79.83; H, 9.62.
16. Compound **16**: $[\alpha]_D^{25}$ +5.24 (*c* 0.76, CH_2Cl_2); IR (film) ν_{max} 3020, 1703, 1525, 1398, 1215, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 3H), 1.49–1.72 (m, 2H), 1.84–2.15 (m, 2H), 2.81–2.97 (m, 1H), 5.52–5.81 (m, 2H), 6.45 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7, 22.1, 31.4, 44.2, 45.3, 126.6, 128.4, 130.2, 149.6, 209.3; GC–MS (*m*/*z*) 164 (M^+), 149, 136, 121, 107, 91, 77, 55, 40; Anal. Calcd for $C_{10}H_{12}O_2$ (164.20): C, 73.15; H, 7.37. Found: C, 72.91; H, 7.55.
17. Compound **17**: $[\alpha]_D^{25}$ +6.27 (*c* 0.35, CH_2Cl_2); IR (film) ν_{max} 2976, 1732, 1455, 1113, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 3H), 1.33–1.62 (m, 2H), 1.99–2.40 (m, 4H), 2.61–2.80 (m, 1H), 4.02 (s, 4H), 5.48–5.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 24.0, 29.1, 31.8, 34.5, 37.3, 76.2 (2C), 116.3, 127.5, 128.4, 218.3; GC–MS (*m*/*z*) 208 (M^+), 180, 178, 165, 151, 126, 113, 105, 91, 69, 65, 41; Anal. Calcd for $C_{12}H_{16}O_3$ (208.26): C, 69.21; H, 7.74. Found: C, 68.98; H, 7.62.